Volume XXI Number 12

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

DECEMBER
1960

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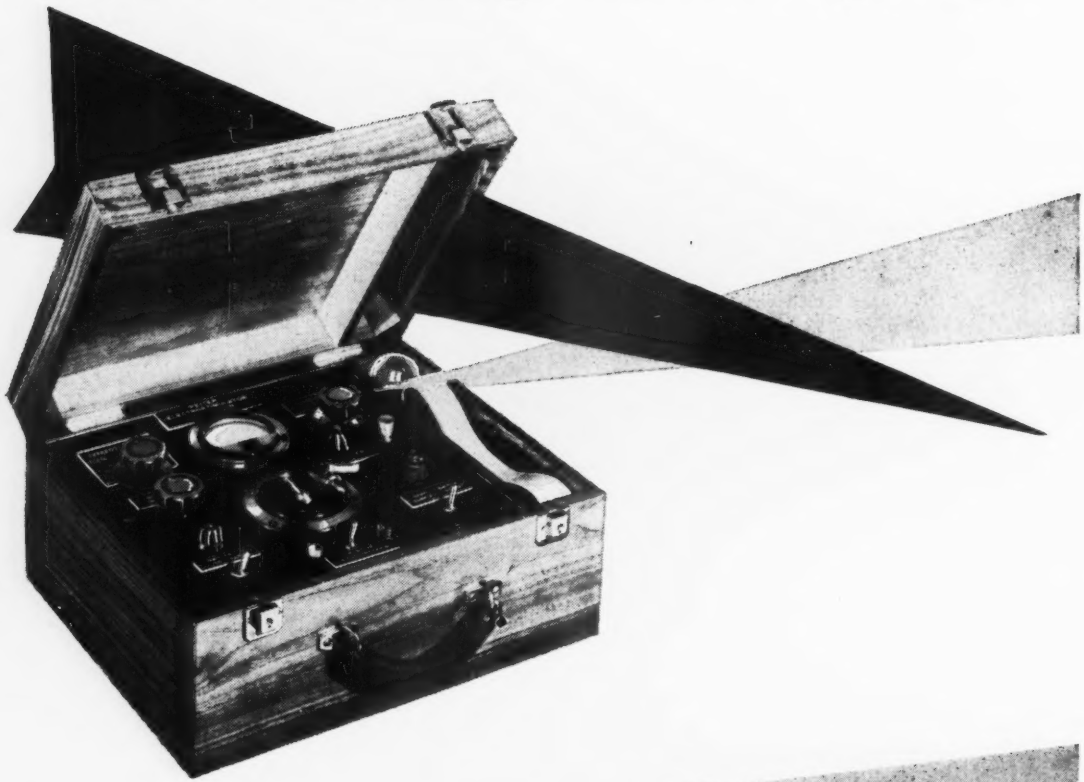

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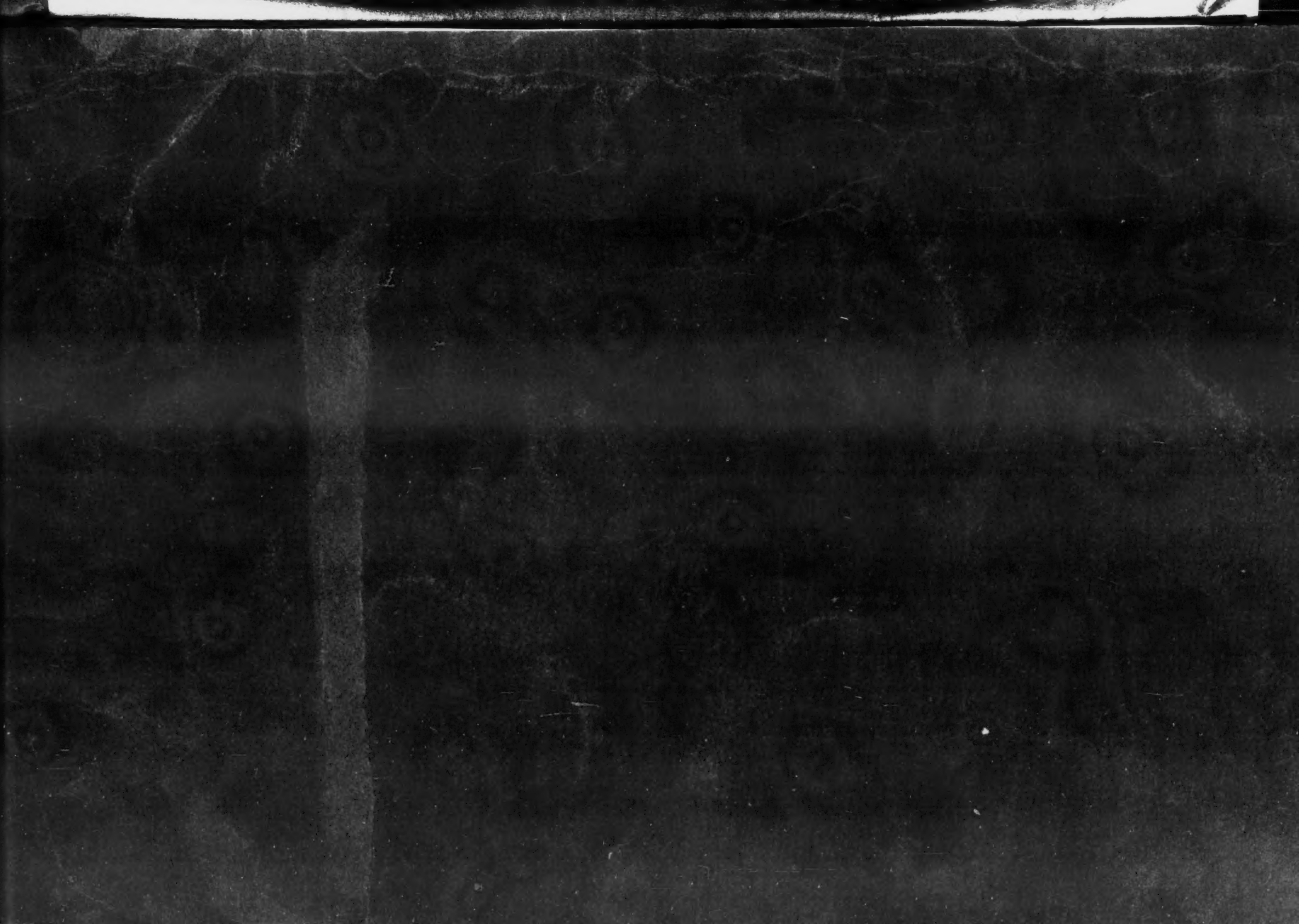

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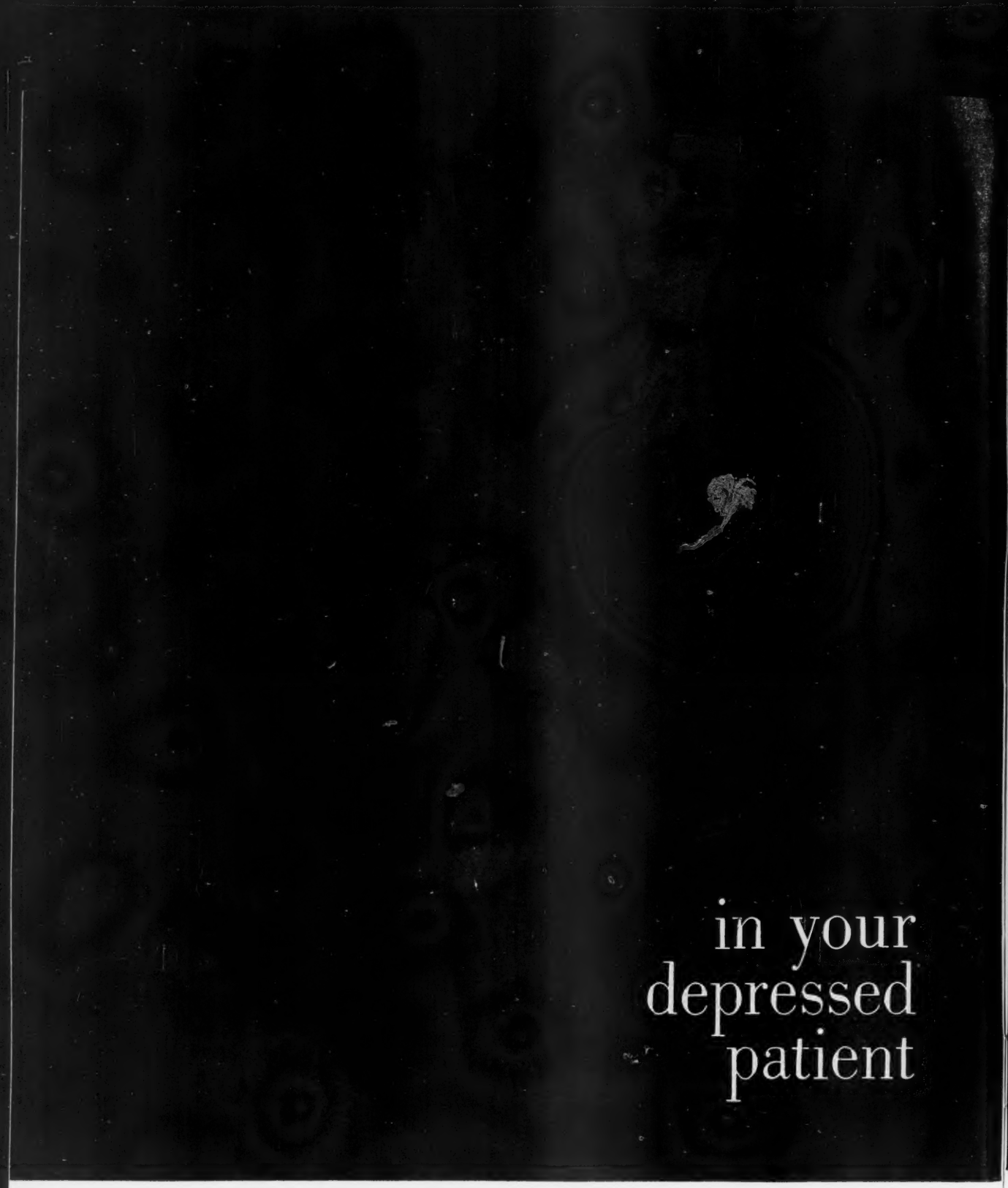

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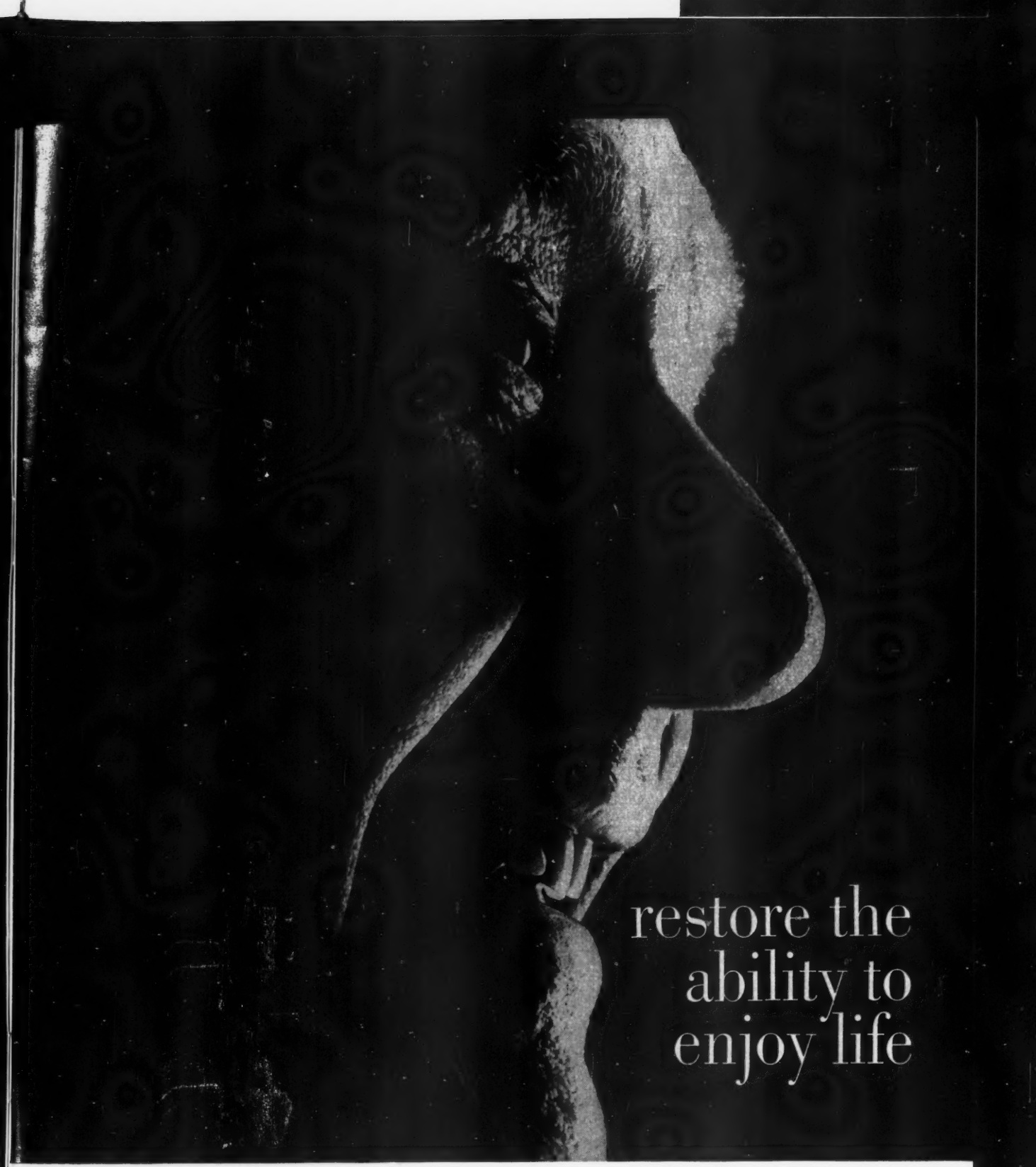

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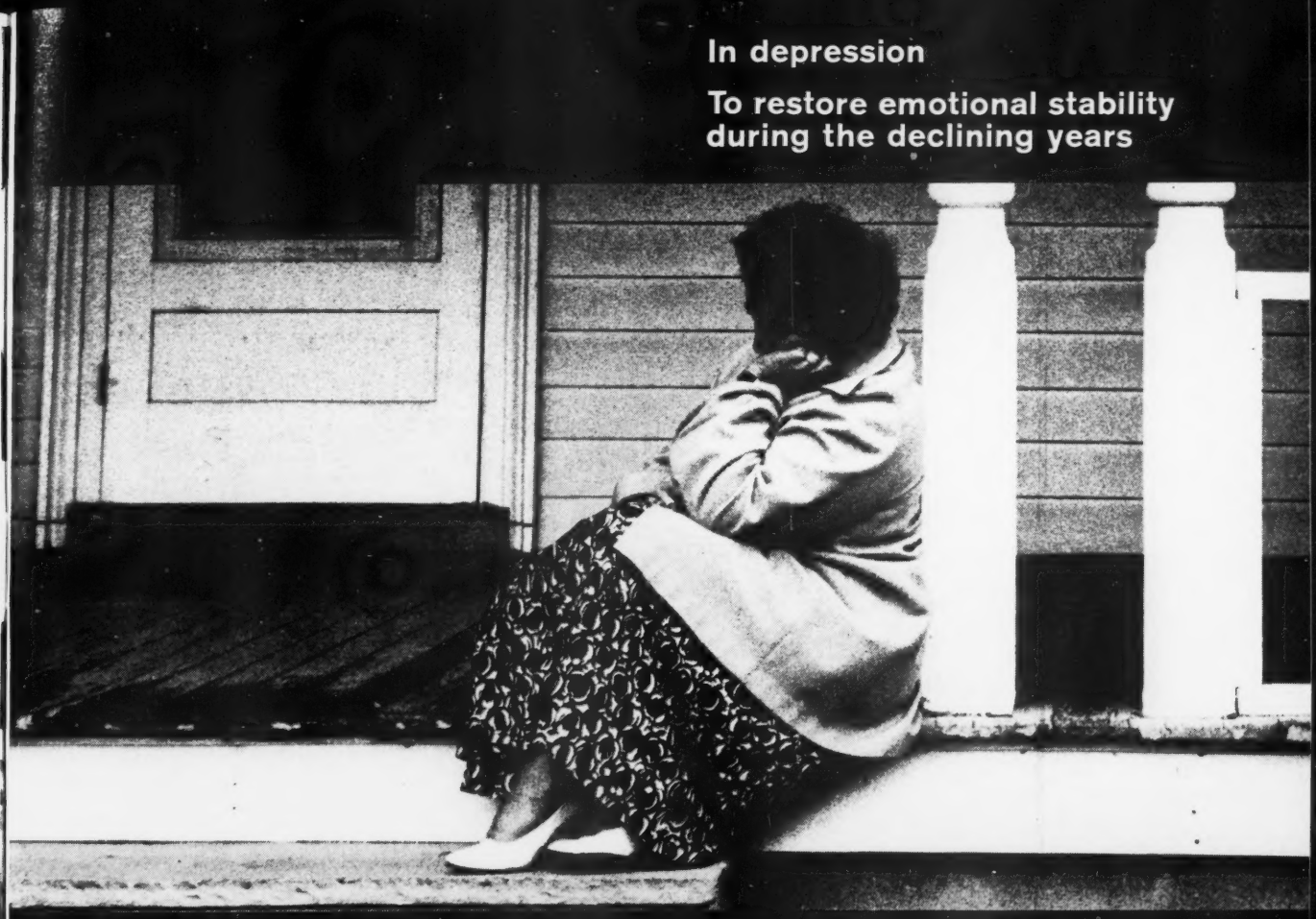

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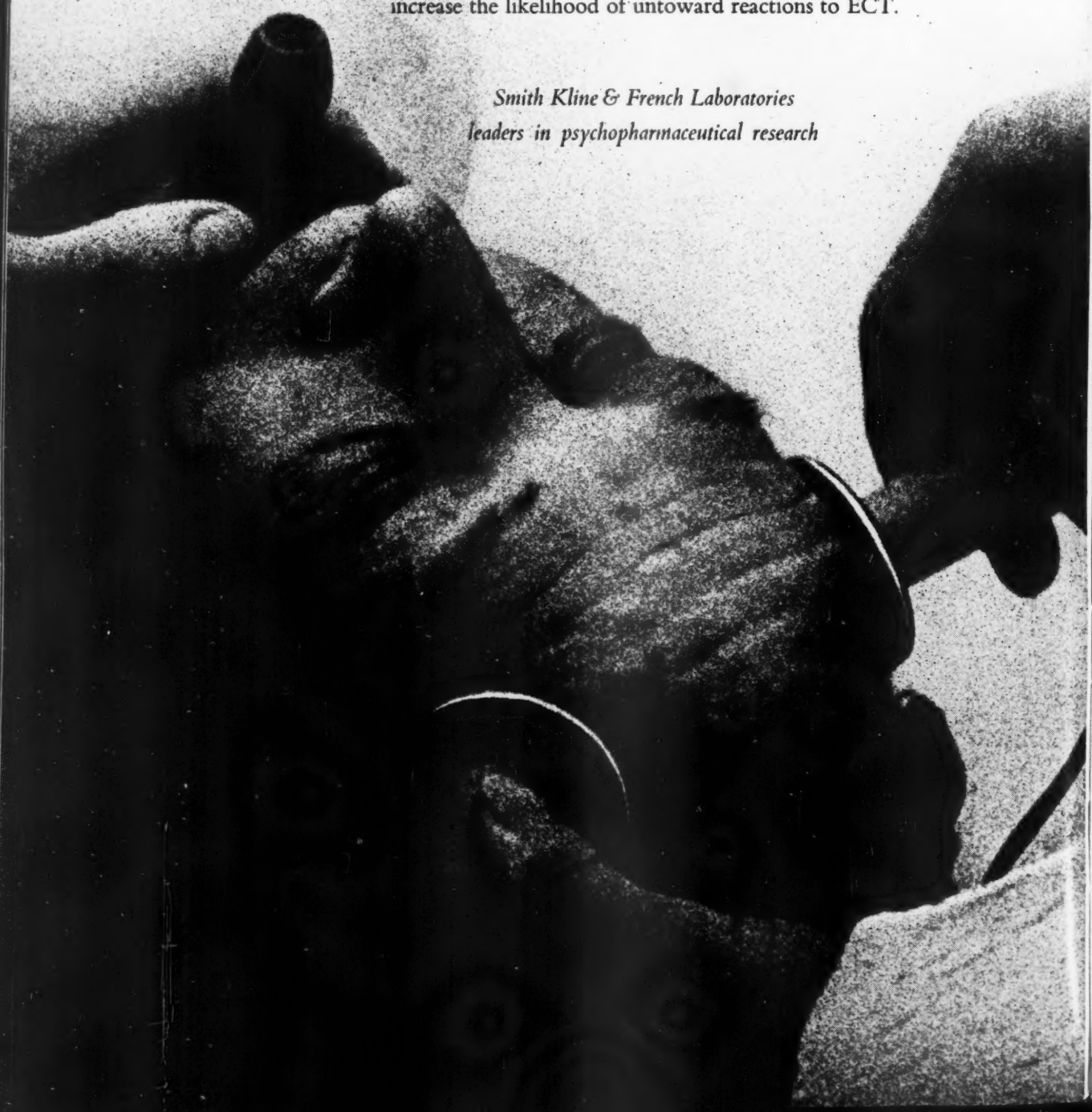

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Factors in Behavior of Certain Epileptic Children

ALICE CALVERT ROBERTS, SC.D., SEYMOUR METRICK, M.D., and JANET ROWLEY, M.D.

The realization that the thyroid gland is in some subtle way related to intelligence is a belief as ancient as Paracelsus. But the sensitive means of testing this specific mental defect which accompanies hypothyroidism took hundreds of years to develop. By the late Renaissance (1603) Paracelsus[1] had pointed out that goiter was often accompanied by simple-mindedness. In his monograph on *Diseases That Deprive Men of Their Reason,* he describes and notes the relationship between cretinism and endemic goiter.[2]

By 1656, Platter[3] had related both simple-mindedness and infantilism to his description of the cretin. He says that "in these infants, we see the indications of simple-mindedness soon after birth" and mentions these children's "inability to learn to speak sensibly" or to concentrate on learning. By 1850, Curling[4] observed the absence of thyroid in two cretins. Gull (1873) mentions that a cretinoid state (myxedema) may occur in adult women.[5] In 1888, another frequent accompaniment of hypothyroidism was reported to the Clinical Society of London. This paper pointed out that irritability, delusions, and other psychiatric manifestations often were present along with the intellectual impairment. "Myxedematous Madness" became a common expression[6] for some of the behavioral symptoms seen in hypothyroidism.

"Though patients often are intelligent, they have slow reaction time, and complain of impaired memory. They oftentimes are apathetic and lethargic. Occasionally they present the picture of manic depressive psychosis usually corrected by administration of thyroid. Deafness is not uncommon."

The literature through the next years piles up the association of psychiatric difficulties that are observed to accompany thyroid ablations or hypothyroidism which is naturally occurring.[7-11]

One wonders why the state of thyroid activity has not been more thoroughly explored in certain childhood epilepsies (notably "14 and 6,"[12] occipital[13] or parietal focus) in which intellectual impairment and behavioral problems frequently are coexistent.

A recent paper by Roberts[14] reviews the present status of literature in the field of electroencephalographic studies and intelligence.

Material and Methods

Subjects

The 22 children chosen for this pilot study were patients referred either for their epilepsy and/or alexias or behavioral problems to the Consultation Clinic for Epilepsy at the Neuropsychiatric Institute of the University of Illinois or to one of us as private patients. They ranged from seven to 14 years of age and carried the "14 and 6" seizure pattern attributed to diencephalic epilepsy in their electroencephalograms. Many of the children had overt seizures. Some did not, but were referred to the neurophysiologist-psychologist because of their behavior or failure to learn in school. Their intellectual disabilities were evident in the field of the language function, alexia, acalculia, agraphia and/or disorders of speech which might be associated with complete withdrawal resulting in little or no ability to communicate). With several of these chil-

dren there was a question whether they were able to perceive in the auditory or visual area, as the case might be.

Some children appeared unmotivated to perform their daily tasks and were said by the parents to dawdle constantly, and by the teachers, to have extremely poor attention spans. Many would not remain seated but insisted on wandering about the room. Many were referred for their constant lying, stealing, and truancy, behavior of which they hardly seemed conscious.

Besides their extremely poor intellectual and emotional development, some children were underdeveloped physically and sexually. Some of them were fair children in a family of brunettes.

Psychometric Tests

The *Raven Progressive Matrices* has been found to be a most useful tool in the study of the intellectual disability of some epileptics[13,14] when it was used in studies of occipital and temporal foci.

"For practical purposes it is convenient to take certain fixed percentages of the population and to group people as their scores fall between them. In this way it is possible to classify a person according to the score he obtains as:

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III 'intellectually average,' if his score lies between the 25th and 75th percentiles;
III+, if his score is greater than the median or 50th percentile for his age;
III—, if his score is less than the median.

IV 'definitely below average in intellectual capacity,' if his score lies at or below the 25th percentile.
IV—, if his score lies at or below the 10th percentile.

V 'intellectually defective,' if his score lies at or below the 5th percentile for his age-group."

This test, which has been factored by Rimoldi[16] at the University of Chicago, seems to have many space-perception factors of a complicated nature, some of which are related to the inversion of figures, left-rightedness, problem solving, and the recognition of symbols, without apparent verbal component.

Each child was tested on the "Raven" at the beginning of the study. He was retested at the end of a two-month period on medication. This interval has been shown by Raven to be sufficiently long to avoid any increase in performance from practice effect. Our own observations have confirmed this finding of Raven's.

Learning

When the reading problem was very great, the children believed capable of profiting from it were started on a reading program which employed techniques designed to implement simultaneously, drill in auditory, visual, and kinaesthetic perception of symbolic language through cursive writing. For example, even children very resistant to writing can almost always be persuaded to attempt to make an *enormous* "a," first passively in the air, then with a big black crayon on newspaper. From this, it is simple to form the word "at" by adding a "t." "An," a second word, is not difficult for these children to form with guidance. Next, the child is encouraged to make these two words, over and over, always spelling them and *sounding* them out until he readily distinguishes between them. In recent years, educators have avoided such drill, but actually the handicapped child seems most anxious for the sense of security that is produced when he develops the skill to distinguish and write these two words. The next step is to form new words on the base "an" and "at" by consonant substitution. These are written, sounded, and spelled over and over, and it has been found that this "game" of writing, spelling, and sounding new words has been very successful as a beginning, to instrument reading in these particular children, whose ability to have symbols become meaningful has been abnormally prolonged. For the first time the child finds himself recognizing, writing and spelling many words. From this point, most of the rest of the alphabet usually can be easily learned and the

new words in a preprimer written for drill in recognition. Series of large cards in the "reading" of consonant substitution on other bases besides "at" and "an" are now used, and as all new words are presented in the preprimers and primers, they are written many times until recognition is established. At first, the task may seem unrewarding, but when the child finally finds himself in possession of these long overdue skills, the satisfactions can bring unbelievably gratifying results. To evaluate the child's progress, Gray's reading tests were used by us, but where the evaluations were made objectively by the National College of Education or the Reading Clinic at the University of Chicago, the tests of their choice were employed.

The *Basal Metabolic Rates* were determined in the clinical laboratories of the Research and Educational Hospitals at the University of Illinois.

Medication

In cases where the B.M.R. fell below the median "0," the patient was put on 5 mcg. L triiodothyronine daily for two months, after which interval the child was again tested on the "Raven."

Results

Raven Intelligence Scores (Tables I and II)

Six children with "14 and 6" seizure pattern electroencephalographically and with alexias, agraphias, and deficient Raven scores (grade V), were placed on 5 mcg. L triiodothyronine (T 3) and trained by special techniques (see method described above) for a period of two months when they were again tested on the Raven. In every case but one (M.D. age 13) the Raven score increased at least one grade level and in three cases it increased two grades, changing the child's rank from *"deficient"* to *"average."* When M.D. was finally receiving two times 25 mcg. after six months, his Raven also rose almost two grades (III—) or to "low average." This change was also confirmed by the testing done at the National College of Education where his Bellevue Wechsler score rose from 72 to 88 in the interval of a year between evaluations. Spot evaluation by objective testers such as this were made, wherever possible, on other children on medication and training. In every instance our

TABLE I

"14 and 6" Epileptic Children With Raven V (Intellectually Deficient)

Age	Patient	Sex	B.M.R.	Raven I	Raven II
7	G.S.	M	—24	V	III+
10	R.M.	M	—20	V	III
11	C.G.	M	— 9	V	III
12	M.K.	F	—21	V—	IV+
12	C.W.	M	—16	V	IV+
12	M.D.	M	—13	V—	V—
			Average —17		

These six children, one girl, five boys, who originally scored in the lowest Raven group were all poor to non-readers. All were put on L triiodothyronine, 5 mcg. daily for at least two months. All raised their Raven scores except one. One raised his score over two points, two at least 2 points, two, 1 point. All now read. Improvement up to two grades in four months.

TABLE II

Epileptic Children With Raven III (Intellectual Average)

Age	Patient	Sex	B.M.R.	Raven I	Raven II
7	R.S.	M	—19	III+	I
8	K.J.	M	—16	III—	III
9	R.H.	M	—11	III—	III
9	P.M.	M	— 6	III+	II+
11	G.W.	M	—13	III—	IV
14	K.N.	F	— 1	III—	III—
			Average —11		

These six children, five boys and one girl, who originally tested average on the Raven all read, were put on L triiodothyronine, 5 mcg. daily for at least two months, and retested. Scores of four were raised, one stayed the same, one fell. No training (visuo-spatial) was given to these children.

TABLE III

Control: Children From Epilepsy Clinic No Teaching and No L Triiodothyronine

Patient	Age	Sex	Raven I	Raven II
E.W.	14	F	III	III+
S.C.	14	F	III+	III+
C.F.	10	F	V—	V—
D.K.	9	M	III+	III+
K.G.	10	M	III+	III+
G.B.	7	M	III	III—

All scores but two remained same. One increased and one decreased slightly, but each remained within the average group. This stability is to be expected, since Raven has shown there is no "practice" effect if two months elapse between tests.

own evaluations on these children's improvement were confirmed by other institutions even though the means of evaluation might be different. For example: the principal in the school of the six-year-old child (G.S.) who had been unable even to distinguish *Jane* from *Linda* when he came to us after a year in school, reported after six months combined therapy that the child is progressing normally for his age and is no longer a behavioral problem—in fact, he states, "We would not know anything had been wrong."

M.K., who was considered to have reached her upper limits of achievement by her school and whose I.Q. was adjudged by them to be 63 on the Otis, is reported by her school to have progressed thus in a year:

	Par. Mean	*Word Mean*	*Arith. Comp.*
Year ago	2.5	2.1	3.4
Now age 13	3.2	4.4	4.9

Another child with different EEG, but one which we find is related to similar problems in reading ability and in the Raven score (bioccipital foci) was evaluated at the University of Chicago. This non-reader (R.B.) is especially interesting in that he was evaluated for his reading ability before he received T3, but after several months on the training program he was still considered by them to be a non-reader at that time. After three months more training and 5 mcg. T3 daily he was then adjudged by the same objective observer, who did not know of the changed regime, to be reading at grade 2.3. This child then received no special training for about six months. After six additional months of combined therapy, the University of Chicago evaluated this initial non-reader at grade 3.9 at 11 years of age. In two years minus six months he went from 0 to 3.9. He no longer is a behavior problem. He had been on two times 25 mcg. approximately three months prior to the last tests. (See Table IV.)

Table II: Control—Children on T3 But Without Teaching

Six other children with "14 and 6" seizure pattern but with little or no reading disability and whose Ravens fell within average range were put on 5 mcg. T3 daily and received no training. One increased his Raven score from grade III (average) to grade I (Intellectually superior). One rose from low average (group III—) to average III. One remained constant (R.N. age 13) and one emotionally disturbed child (age 11) fell from low average III— to IV (below average).

TABLE IV

No L Triiodothyronine; Training Only (Two Months)

Age	Pt.	Raven I	Raven II (2 Mos. Later)	3 Mos. Later On T3
11	J.T.	V	V	—
9	R.B.	Non-reader*	Non-reader*	Reading 2.3*

*University of Chicago evaluation.

R.B. had not read even with three years in special classes. He only learned nine words for recognition in two months intensive training. After three months combined therapy he read 2.3 and in two years minus six months he has advanced to 3.9 (again tested by University of Chicago reading clinic).

Table III: Control—No T3, No Training

Three of these children were originally tested three years prior to the second test, yet their scores remained practically constant. One out of six showed a slight fall. The constancy of score was Raven's finding also in large numbers of control subjects when at least two months elapsed between tests.

Table IV shows two cases on training alone for two months. Results in one (J.T.) shows a Raven score which did not change with training alone, and the other (R.B.) a reading score tested by University of Chicago reading clinic. The last named patient did not become a reader until after he was put on L triiodothyronine for three months. He had had special help at school for three years before this time. Many more children must be studied to definitely identify the effects of the special training and the T3. However, this paper merely tries to report the progress that can be made with such children in combined therapy when these means of diagnosis are employed.

Table V shows the tendency of these children to have low B.M.R.'s. It is noteworthy that many of the problems which are en-

countered in doing B.M.R.'s would tend to raise them rather than to lower them.

Tables VI and VII. The high incidence of abnormal electroencephalograms in the three families available for study is provocative as is also the high incidence of other physical abnormalities and hypersensitivities.

TABLE V

Basal Metabolic Rate of Certain Epileptic Children With "14 and 6" Pattern Electroencephalogram

Patient	Age	B.M.R.
A.C.	13	— 9
C.G.	11	— 9
K.J.	8	—16
E.J.	11	x
M.K.	12	—21
J.H.	14	— 7
R.S.	9	—19
W.S.	11	— 9
M.B.	8	—14
K.N.	14	— 1
M.T.	14	— 9
P.C.	12	— 6
R.M.	10	—20
C.W.	12	—16
L.W.	12	+ 6
M.D.	12	—13
G.W.	11	—13
J.I.	10	— 1
M.L.	10	—20
P.M.	9	— 6
E.W.	9	—14
R.H.	9	—11
G.S.	7	—24
C.F.	10	—11

Discussion

This paper deals with a pilot study of a particular epileptic group, "14 and 6" with problems in behavior and/or in learning as related to the language function. Table V shows in this present study referred for reading and behavioral problems all of the children had B.M.R.'s below the median "0," and that the children in our group who had Raven scores "V" and grave reading problems, had B.M.R.'s below "normal." (Table I.)

The lengthening of the attention span of these children on both L triiodothyronine and a teaching program is perhaps the most dramatic and detectable improvement, and may be a most important factor in their increased ability to learn through both auditory- and visual-perceptual channels. Also several "withdrawn" individuals became openly communicative and related well to their surroundings after medication. (Letters from camp and school indicated this change in one patient—K.N.) Another two year old adjudged autistic is beginning to communicate with the counsellor, and a pre-

TABLE VI

Three Families

	Age		Patient	B.M.R.	E.E.G.
I	16	J.N.	Rheumatic Fever	—13	14 & 6
	14	K.N.	Epileptic Personality	— 1	14 & 6
	12	K.N.	Patient	— 3	14 & 6
	5	P.N.	Rheumatic Fever	–	14 & 6
II	18	E.K.	Jaundiced at Birth, Asthma	–	–
	16	R.K.	Normal Mentality, Jaundiced	—17	Normal
	14	M.K.	Jaundiced (?)	—7 & —11	Psychomotor variant
	13	M.K.	Asthma (patient), Epilepsy, C.P., Jaundiced	—24	14 & 6
(twins)	11	D.K.	Normal	+ 6	Normal
	11	J.K.	Mongoloid, Jaundiced, M.D., Heart	–	–
III		E.J.	Epilepsy, C.P., M.D., Speech, Asthma	–	14 & 6
		K.J.	Asthma, Epilepsy	—16	14 & 6

High concentration of: 1. Abnormal EEG's.
2. Low basals.
3. Hypersensitivities, mental and physical ills or handicaps.

Eight out of ten records obtainable had abnormal electroencephalograms or 80% at least. (Two were not obtainable.)

TABLE VII

Cluster of Abnormalities Found in Twelve Siblings in Three Families Studied Electroencephalographically

1. ELECTROENCEPHALOGRAMS

Normal	*"14 and 6"*	*Other Abnormalities*
2	7	1

80% of the ten electroencephalograms obtained were abnormal.

2. HYPERSENSITIVITIES

Asthmatic	4
Rheumatic	2
Cerebral Palsied	2
Mongoloid (twin normal)	1
Speech Defective	2

viously untestable cerebral palsied child with little or no speech, who was so uncooperative at eleven years that no B.M.R. could be obtained, now attends to the Raven long enough to select the first five items and names 17 of the 18 Binet vocabulary pictures although initially he was almost speechless. These cases do not show in the tables, but their improvement is just as important as those who fall into groups which it is possible to test on the Raven because of their higher levels of intelligence.

Only one child (M.D.) put on the combined reading program and L triiodothyronine for two months failed to raise his Raven score. Some raised their scores very appreciably so that they went from a deficit intellectual score, Raven V, to average, Raven III, although Raven has shown and Table IV demonstrates that after two months, practice effect is not a factor in this increase, but that this score usually remains quite constant through the years.

This one child (M.D.—13 years) who failed to change his Raven score on 5 mcg. L triiodothyronine daily, actually improved in reading and writing skill under the regime. In about four months he went from grade III to grade V in reading score when his progress was judged by an objective observer. This particular child's deficit in spatial perception had amounted almost to a spatial disorientation which showed in his extreme difficulty in learning right from left, and the relative positions both on the vertical and horizontal axis of places on a large map. His finger agnosia was very marked.

One child (R.B.—9 years) had been tested at the University of Chicago laboratories, where he was adjudged a non-reader, after two months training *without* medication. After three months combined medication and training, he was reading at grade II level according to their evaluation. In the same laboratories he showed his increased attention span by his persistence at his reading test for almost two hours, although the examiner assured him he was welcome to stop at any moment. In the two months previous to medication, only nine words had been learned, so it is believed that medication was instrumental in this changed learning ability. The person who teaches knows the help this medication can give to facilitate learning! The child's barrier to seeing and hearing symbolic language changes in these specific cases, and this visio-spacial perceptive change is usually shown by his increased score (Table I).

Needless to say, a child who suddenly finds himself in possession of reading skills and able to "see" symbolic language often loses some of his behavioral difficuties. At least apparent motivation and dawdling usually changed in these children in regard to other activities as well as to reading. However, educationally and in planning their education it is a mistake to believe that they quickly and completely have made up several grades of school because they can now handle the reading of symbolic language at a considerably higher grade level than previously. The child must be placed in a grade at a level at which he is capable of functioning and where reading is still being taught at his level in order that he may not be further traumatized and frustrated.

A concomitant of these children's lack of reading ability (Table I) is their inability and unwillingness to write. Often an educator will say, "Of course he can't write, because he can't read." This statement should probably be reversed for these children. Many of their problems such as this one,

stem from their confused visuo-spacial disorientation, which also appears as a "finger agnosia." Not only is the image reversed on the horizontal axis, but in the vertical axis as well in some children. Where it is left and right, time orientation comes into play so that if these children write the word "saw," "s" is written before "w." Whereas in reading, "w" might have been *seen* first. Therefore, writing the words they need to learn helps them to see in the right order. Initially, these same children often match horizontal and vertical lines in the Raven, a rotation of the visual axis of 90°, but after training, they usually do not perform in this fashion.

Physiological

Since a common complaint of the "14 and 6" group is nausea, vomiting and headache, and since the B.M.R.'s had a tendency to be low where there is marked reading disabilities, it is suggested that the physiological mechanism may be related to the mountain sickness syndrome sometimes suffered by certain individuals at high altitudes where the partial pressure of available oxygen is low. The end result might lower the oxygen supply to the tissues themselves. Of course, the low B.M.R. is only an indirect indicator that the available oxygen in the tissues may be somewhat low, but often where the visuo-spacial perception was poorest (Raven V) the trend of the B.M.R.'s was lowest. (See Table I.)

It is true that some of the low B.M.R.'s were found in children who had been on other medication, and the effect of this would have to be ruled out. However, when other children with "14 and 6" were first placed on similar medication, their B.M.R.'s were not found to be altered.

The two children with the lowest B.M.R.'s were both asthmatics, as were many of the children in our study. One of these children was jaundiced and one was cyanotic at birth. There was a high incidence of asthma and other hypersensitivities such as Rh incompatibility resulting in jaundice, and rheumatic fever. Directly or indirectly these hypersensitivities may be contributory to oxygen deprivation in the tissues, i.e., anaemia associated with jaundice or circulatory disturbance in rheumatic fever.

Since oxygen deprivation has long been accepted as one etiology of many mental and physical handicaps and since hypersensitivities may result in jaundice (Rh factor) and respiratory manifestation (as asthma) and impaired circulation from rheumatic fever, indirectly increasing the degree of oxygen deprivation, it would seem that hypersensitivities could be playing an important role in the etiology of many of our handicaps. Hypersensitivities tended to cluster in the families of our patients to an abnormally high degree as well as frequently being overtly present in the patients themselves. It is notable that hypersensitivities have been found to cluster in another group of epileptics studied, hypsarhythmia (unpublished); Table VI shows the incidence of asthma and rheumatic fever in three of our families in this study of "14 and 6." (Several electroencephalograms were not available and in severe mental retardation we did not secure B.M.R.'s.)

There is no study of normals which covers just the hypersensitivities we frequently encounter (asthma, hay fever, rheumatic fever and Rh factor) in patients and their families. But Swartz's[17] 1.31% incidence of asthma and hay fever combined in a normal population and his quotation of 8% in a study of over one thousand college students contrasts markedly with the incidence of asthma, hay fever, Rh factor, and rheumatic fever we found in the families of our patients. Also in this study of three families (Table VII) we found only two normal electroencephalograms in eight patients and siblings. Seven out of ten of those electroencephalograms available for study were "14 and 6" (70%), in marked contrast to the finding of the Gibbs of 2½ per cent in a "normal" population[12] quoted in an early study, with some increase over that figure in an age group comprised of children in late adolescence. (Gibbs—unpublished personal communication.)

The children's handicaps in these families included personality disorders, mental retar-

dation of various degrees, mongolism and cerebral palsy, besides their epilepsy. It would seem then that certain handicaps also cluster in these families in high degree. The children are frequently reported jaundiced at birth (four out of six children in one family). Bilirubin inhibits the respiratory enzymes of mitrochondria.[18] It also inhibits the formation of heme, "the prosthetic group of numerous enzymes essential for biological oxidation."[19] In this "14 and 6" category of epilepsy as well as in hypsarhythmia group, cyanosis at birth is frequently mentioned, particularly in those families with asthmatic history on both maternal and paternal sides.

It would appear that many of the vague complaints of these children, their pains, nausea and vomiting, could be on the basis of their need for increased oxygen related to their hypersensitivities and concomitant epilepsies even when the latter does not manifest itself in the form of convulsions and blackouts.

It is possible that the efficacy of L triiodothyronine plays an unknown role in the development of the central nervous system by supplying needed chemicals such as an enzyme, for continuing use. Our limited experience does not indicate that these children's progress reaches a plateau and stops, but that with continued optimal opportunities for their specific educational needs, they are, so far, continuing to progress. In the cases of older children dosages have been adjusted for weight and age and usually have reached 2 x 25 mcg. for several months. At this point pallor and skin tint often shows a marked improvement and the personality of the children becomes lively—may we describe this as a sense of humor? Much is still left to be done to verify the evidence so far accumulated. Optimal dosage must be established, and other thyroid entities (i.e. tetra form) besides the L triiodothyronine form (T3) which we employed should be tested on similar patients and related groups, especially those cases who have other disturbances of language function, i.e., speech defects, as we have found indication that the drug has been effective in this area. Setting up normal controls or preferably optimal standards from among groups of children exhibiting excellent health, both mental, physical, and emotional, for future comparison, is a very necessary step to be undertaken in the near future. Then comparisons of chemical entities and other laboratory findings could be made on a much sounder basis than was possible in this present pilot study.

Better means of determining the diagnosis of hypothyroidism will be attempted, i.e., circulatory impairment, dusky pallor, retardation of growth and development, but not "fatness." This last named entity Wilkins found in only three of his 200 hypothyroid patients.[20] Finally, it is proposed to carry out arterial blood gas analyses, similar to those being done by Dr. Manuel Meir in the study of parkinsonism.[21]

Conclusions

1. Many more boys than girls are referred for serious reading disabilities with "14 and 6" seizure pattern.

2. With or without teaching, the Raven scores of ten patients out of 12 improved on L triiodothyronine 5 mcg. daily for at least two months, although Raven scores do not generally improve if a two-month interval is allowed to elapse between tests.

3. Both patients who did not improve their scores were at least 11 years of age. The dose may have been inadequate for them either because of size or age or both. One of these children's score increased to low average when placed on 2 x 25 mcg. T3 after six months.

4. In spite of their low Raven scores and early difficulties, all children in this study learned to read or advanced several reading grades in four months on the combined therapy of L triiodothyronine and special education.

5. There is a high incidence of "14 and 6" in the families of these children and an extremely high incidence of hypersensitivity.

Authors' Notes: Opinions expressed in this paper are not necessarily those held by the Department of Electroencephalography at the Neuropsychiatric Institute of the University of Illinois but are those of the authors.

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Psychopharmacology and the "Deteriorated" Schizophrenic Patient

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The long term, "deteriorated" schizophrenic whose total activity seems to have been reduced to gastrointestinal tube function is a special problem in psychopharmacology. For decades he has existed in what appears to be an irreversible end stage of his disease. He has defied innumerable therapeutic efforts. The opinion was recently offered that "the severely deteriorated, withdrawn, vegetating, chronic, psychotic patient does not respond well to any of the tranquilizers, or unfortunately, to any other therapy we have available today."[1] Although it is true that the hyperkinetic, assaultive, disturbed patient provides a more favorable test of the ataractics, those showing maximal constriction of affect and behavioral regression can also benefit. In our experience and that of others[2] a certain number of these patients will become mobilized, alert and in contact during a consequential course of phenothiazine therapy. However, to be effective, drug therapy must be administered under special conditions.

Relatively large amounts of the phenothiazine must be administered. Doses far in excess of those commonly recommended are sometimes required. These large amounts of drug are surprisingly well tolerated without encountering jaundice or agranulocytosis. After autonomic adjustment to the first doses, the drug induced extrapyramidal syndrome (EPS) becomes the major problem.

The tranquilizer must be administered for

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Supplies of thioridazine (Mellaril) were obtained from Mr. Harry Althouse, Sandoz Pharmaceuticals, San Francisco, California.

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many months before failure can be presumed. We have observed individual patients who showed no definite favorable change in their condition until a half year had passed. Only then did they slowly begin to emerge from their maximally withdrawn, demented state.

Occasionally, individual patients in this category will respond to one phenothiazine and not another. Therefore, a trial of more than one tranquilizer is warranted before the patient can be considered a nonreactor to drug therapy. The assumption that the phenothiazines with a ring structure in the side chain is preferable for the apathetic, unmotivated schizophrenic is not justified.

Minor details may defeat the therapeutic trial. For example, 10-15% of negativistic patients "cheek" their pills occasionally or habitually. The swallowing of medication must be carefully supervised. In a consistent simulator who feigns swallowing his medication, a liquid preparation should be substituted.

A plan for restructuring the established maladaptive modes of coping with life stress and interpersonal relationships must be available for the psychotic patient once he has been mobilized with the psychoactive drugs. This combined pharmacologic-psychologic approach maximizes the improvement and prevents relapses. Through a therapeutic community or other resocialization program he can begin to make healthy human contacts, to initiate planned, purposeful, gratifying activity and to gradually accept a degree of responsibility and freedom. Many of the patients in our study were unable to participate in a patient community project until they had first been relieved of disrupting preoccupation with drugs.

The majority of the patients in this category require long term, if not perpetual, maintenance drug therapy. The dosage levels are only a fraction of the amount required for initial improvement. Tolerance does not occur. Side effects are extremely uncommon during the maintenance period. The maintenance level is the smallest possible amount that will retain the gains achieved. Periodically each patient should be studied for the purpose of adjusting dosages rather than permitting an established schedule to continue indefinitely.

During the maintenance phases patients can be managed satisfactorily with medication once or twice daily regardless of the preparation used. We have successfully maintained some patients with five doses a week permitting drug-free weekend visits away from the hospital.

For the past six years the effect of a series of phenothiazines on anergic schizophrenics has been under investigation. Of those evaluated, chlorpromazine, prochlorperazine, triflupromazine and trifluoperazine have been found to be satisfactory agents. During the past two years thioridazine (Mellaril) has been given to 200 patients of this category. Many of these were prior treatment failures or had had toxic effects with other phenothiazines. Thioridazine may well have certain advantages when intensive and extensive therapy is necessary because of the extremely low incidence of extrapyramidal discharges or serious side effects. The equivalent dosage-time-response ratio for thioridazine is more favorable than for other phenothiazines. When necessary extremely large amounts (2-3 gm. daily) could be given without encountering disabling toxic effects. It was noted that these large doses were infrequently required with thioridazine.

The schizophrenic has gross disturbances of body image; in fact, the syndrome can be understood as a disorder of self concept and ego boundaries.[3] Chemically induced parkinsonism further distorts motor control and makes the sensory cues which are required to maintain reality orientation imprecise. For this reason we consider the EPS to be an undesirable and antitherapeutic complication. We have routinely prescribed antiparkinsonian agents at the onset of high dosage therapy with those more potent phenothiazines having a piperazine ring in the side chain such as trifluoperazine. With thioridazine this has been unnecessary and the incidence of the EPS is lower than with any other analogue that has been studied here.[1] By decreasing the dosage and building up the amount of thioridazine more

slowly it has been possible to control the EPS in all patients but one without antiparkinsonian drugs.

Thioridazine was found to be approximately equipotent to chlorpromazine. Weekly maintenance levels varied from 700-9800 mg. Whenever "cheekage" was suspected or detected, the adroit nonswallowers of medication were given a liquid concentrate (30 mg. cc) of thioridazine which is available.

Table I reports our estimate of the results of 6-24 months of thioridazine therapy.

TABLE I

	Patients	*%*
Definitely improved	79	39.5
Slight or questionable improvement	98	49.0
Unchanged or worse	23	11.5
	200	

The definitely improved group demonstrated unquestionable change with 14% being able to leave the hospital, and the rest remaining in the hospital at the time of this report but functioning in a manner distinctly better than their performance of past years. A number could be discharged but for the fact that the relatives and family have disappeared or have completely dissociated themselves from any relationship with the patient. Suitable foster homes are being procured for these individuals, funds permitting. The ability to perform work details, manage ground and pass privileges and participate in group activities were some of the objective evidences of substantial improvement. With a large segment of the ward demonstrating behavioral progress the character of the service changed so that one half of the building could be opened for the first time. It is to be recalled that we are speaking of patients who had previously been described as dilapidated, deteriorated or demented and whose schizophrenia first required hospitalization an average of 15.2 years before the thioridazine course was started.

Summary and Conclusions

It is likely that the "deteriorated" schizophrenic does not exist but that his gross mental deficit even after years of psychotic involution remains partially correctible. What is considered dementia represents his failure to correctly apperceive and respond to sense data due to defective scanning of the environment. This, in turn, derives from an inability to distinguish internal from external environment. Successful psychochemical therapy for this group may reconstitute ego feelings and boundaries by screening out intensely disturbing signals from unconscious sources thereby decreasing anxiety and the subsequent withdrawal response. At this point autistic preoccupation diminishes and involvement with external interests and socialization becomes a possibility. Such a patient maintained on his tranquilizing agent can be fitted into a benign community and continue to progress toward satisfactory social adaptation.

The use of the term schizophrenic "deterioration" is a reflection of progressive psychic involution on the part of the patient and progressive despair on the part of his physician. Both processes are partially reversible. In our experience thioridazine is the preferred phenothiazine for this group of patients. Its effectiveness and lack of toxicity at high dosage levels over long periods of time make it useful in the treatment of the end stage schizophrenic.

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Electroencephalographic Changes Following Prefrontal Lobotomy

(Incidence of Frontal Lobe Asynchrony in Deep Sleep)

JOHN H. WILMS, M.D. and VERN M. COLE

Introduction

The purpose of this paper is twofold. First we intend to describe a constant neurophysiological abnormality secondary to a known, artificially created neuropathological lesion. This is an electroencephalographic pattern that appears to follow consistently prefrontal lobotomy. Secondly, we shall attempt to verify our conviction that an electroencephalographic examination is not complete unless a tracing is made while the subject is in deep sleep as well as in the stages of waking, drowsiness and spindle or light sleep. We submit this report with the hope that we may make some small addition of simple but apparently valid data to the growing body of knowledge of the correlation of function with structure of the central nervous system.

EEG changes following prefrontal lobotomy continue to be puzzling although the literature contains many descriptions and theories upon the subject. A prominent 0.5 to 1 per second frontal electrical activity in the waking state has been observed to be of common occurrence immediately after the operation but to decrease in incidence and amplitude during subsequent years.[1,2] The incidence of apparently normal records increases with increasing postoperative time although such reversal to normal is scarcely to have been expected in view of the extensive and presumably permanent lesions produced by the operation.

In 1957, Adams, Gibbs and Gibbs[3] reported that, 36 months after operation, an asynchronous, frontal, slow wave activity invariably was present in deep sleep of the lobotomized patients they studied. For several years we had been making annual electroencephalograms on a large group of lobotomized patients within our hospital. It had been our impression that some of these patients' tracings became normal again some time after the operation. The results of our search for the phenomena reported by Adams, Gibbs and Gibbs constitutes this report.

Material and Method

When this study was undertaken in 1957 there were within the hospital 104 patients who had undergone the lobotomy operation and who were available for examination. These patients had all been operated upon between 1950 and 1955. The shortest postoperative period was two years at the time of completion of the study. These lobotomies had all been performed through bilateral burr holes which were through or immediately anterior to thec oronal suture line. The lobotomy cuts were made just anterior to the ventricles and extended to near the midline, to the inferio-mesial angle and to a varying degree laterally depending upon the extent of the lobotomy desired. There had been no operative accidents or any postoperative symptoms that could be considered indicative of conditions that might cause abnormalities significant to this study in the EEG's. The patients had been and continued to be hospitalized, psychotic veterans. Findings of clinical examinations did not suggest the presence of organic brain damage that might confuse the observations reported here.

A control group of 23 patients was selected from the hospital population at the time of the study. Their ages and diagnoses matched in general those of the lobotomy group; however, they were either not as ill as those of the lobotomy group or they had been hospitalized since the advent of tranquilizing medications which virtually has eliminated the need for lobotomy within the hospital.

The electroencephalographic records were all made on an eight-channel electroencephalograph with monopolar leads. Technique

and interpretation were according to descriptions and standards illustrated in Gibbs' *Atlas of Electroencephalography.*[4] Deep sleep was spontaneous or was achieved by the oral administration of 0.1 to 0.2 grams of Secobarbital. This medication apparently caused some low-voltage, fast activity in the stages of waking and drowsiness, but caused no detectable alteration in the stages of sleep and deep sleep. All stages, from waking through deep sleep were recorded for all patients included in this study.

Each patient of the lobotomized population had been examined electroencephalographically annually since the operation. A review of the 1957 annual tracings of these patients yielded 16 whose electrical activity was apparently normal in the stages of waking, drowsiness, and in the stage known as spindle sleep. The remainder of the lobotomized group manifested the expected or typical postoperative changes in one or more of these stages.

These 16 lobotomized patients whose electroencephalograms were ostensibly "normal" were then re-examined in the stage of deep sleep. Records were also made during deep sleep on the 23 patients of the control group, all of whose electroencephalograms were apparently normal while they were awake, drowsy, or in the stage of spindle sleep.

Results

Of the 16 lobotomized patients whose tracings were normal while awake, drowsy, and in the stage of spindle sleep, all gave evidence while in deep sleep of the asynchrony between the slow wave electrical activity of the frontal lobes as described and illustrated by Adams, Gibbs and Gibbs. This asynchrony of frontal activity during deep sleep could not be demonstrated in any of our control group of 23 patients.

Comment

It is generally agreed that the frontal lobes in deep sleep manifest electroencephalographically a slow, 0.5 to 1 per second activity, and that the slow waves of the two hemispheres normally appear to be synchronous. It is also known that slow waves similar to those observed in the frontal lobes during deep sleep may, under other circumstances, indicate underlying brain damage which may vary greatly in location.[5] This pathology may exist in cortical layers, in cortical projection pathways, in thalamic nuclei, in the hypothalamus or in regions as remote as the contralateral lobes of the cerebellum.[6,7] It should be remembered also that the abnormal electrical activity may not be due to the lesion itself but to the disturbed physiologic processes of the surrounding tissues.[7]

Since, in this article, we cannot go further into the complexity of the subject, we shall turn to a review of the pathological findings following the lobotomy operation. Greenblatt and his fellow workers[8,9] reported that they found in a group of lobotomized patients the connections between the dorsomesial thalamic nucleus and the orbitomesial quadrants of the frontal lobes were consistently severed in the course of the operation, and that degeneration of fibers could be observed always in the subthalamic region and the rostromesial quadrants of the pons as well. Adams, Gibbs and Gibbs[3] propose degeneration of interthalamic commissural pathways as a possible explanation of the asynchrony they observed.

If the results of lobotomy were constant and were limited to the findings reported above, it would be difficult to explain why patients exemplify variable findings in the wake, drowsy, and spindle sleep stages ofter lobotomy. Pathological examination of lobotomized brains, however, discloses many remarkable and highly significant variations.[8] Preoperative asymmetry of the hemispheres, ventricular enlargement and varying degrees of cortical atrophy render the exact location of the surgical lesions in the cerebrum significantly unpredictable. Postoperative edema, septic and aseptic meningitis and encephalitis may not be detected clinically but are not of uncommon occurrence nevertheless. Their presence is manifested in part by severe gliosis of the frontal cortex that seems to be more severe as the postoperative interval increases. These disorders may appreciably alter the cerebral

metabolism, focally or diffusely. Hemostasis, accomplished by electrocoagulation, metallic clips or ligatures, results in unpredictable but commonly occurring regions of infarction and hematoma in varying degrees of proximity to the surgical field. When these postoperative lesions are considered together, it is evident that the results of prefrontal lobotomy are neuroanatomically uncertain to an important degree.

The asynchrony between the frontal lobe, slow-wave patterns of deep sleep could indeed be caused by degeneration of commissural fibers which tie together right and left thalamic nuclei. Such degeneration might cause the nuclei to project sleep patterns independently to each frontal cortical hemisphere as Adams, Gibbs and Gibbs proposed. Such a hypothesis must yet be proved by post-mortem examination of the brains of lobotomized patients. It is certainly to be desired that the brains of patients with such relatively controlled lesions will be carefully examined, utilizing the best of neuropathological techniques.

Summary

A study was made of 16 patients who had undergone lobotomy and whose electroencephalograms appeared normal while they were awake, drowsy, or in the stage of spindle sleep. In deep sleep, all of these patients manifested the abnormal asynchrony between the frontal lobe slow wave patterns described by Adams, Gibbs and Gibbs. We were unable to demonstrate this asynchronous frontal activity during deep sleep in any of our control patients. Therefore, we confirm the findings reported in 1957 by Adams, Gibbs and Gibbs.

We are unable to offer an adequate explanation of the presence or absence of this phenomena, but we believe that it is related to the injury received by the brain during the lobotomy operation. Postoperative pathological reactions to this type of surgery are briefly reviewed.

There seems to be no doubt that electroencephalograms which otherwise appear to be normal, may give evidence of brain injury if made while the patient is in deep sleep. Such evidence might be a frontal lobe electrical asynchrony or a frontal lobe focus of slow-wave activity. Electroencephalographic examination should not be considered to have given normal results unless recordings are made during deep sleep in addition to the stages of waking, drowsiness, and the so-called spindle stage of sleep.

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Directive Psychotherapy with Parenteral Ritalin in Advanced Schizophrenia

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In individual psychotherapy two different major techniques are in use, depending on the orientation of the therapist. As outlined by Mac Iver and Redlich[1] the non-directive, also called psychological and analytical, is advocated by the dynamically oriented analyst. The directive approach practised by the psychiatrist who emphasizes organic (or physical) treatment, is too often neglected and rejected by the analyst. While the analyst prefers treating the neurotic, the psychotic and particularly the schizophrenic is handled by the organically oriented psychiatrist. The analyst frequently is unsuccessful in treating the schizophrenic, especially the deteriorated regressed individual, because no rapport can be established. If approached by the non-directive method the advanced schizophrenic will continue to indulge in his fantasy and will rarely progress to a level where transference and insight may occur.

In a recent study[2] of the effect of injectable Ritalin (methylphenidate) it was found that stimulation with this drug will make the delusional, withdrawn, unmotivated and regressed schizophrenic amenable to an intensely directive psychotherapeutic approach, eventually capable of rational communication with the therapist and finally able to repress psychotic ideation. It is acknowledged that although the directive method may fail in accomplishing a cure of the mental illness, through insight, it will succeed in a better overall function of the schizophrenic, when suppression of delusional thinking can be obtained. While the analyst in general refrains from the use of narcoanalytic or stimulant drugs, the organicist uses stimulants to achieve catharsis and mood elevation. This is essential in the treatment of the schizophrenic who is difficult to approach because of his hostility and resistance, especially when the mechanisms of the dynamics are unknown.

Ritalin has been used as a cerebral stimulant and antidepressant for some time. While its oral use has a bland effect in psychotherapy, the parenteral uses, particularly the intravenous, often gives a dramatic abreaction. In a recently reported study[2] in which the method of administration was described, it was found that an optimal dosage was 50 mg. (5 cc. I.V.). Under the influence of the drug, alertness, concentration and memory recall are stimulated and hostility, depression and anxiety reduced. Often new perspectives for the treatment are given by the release of psychodynamically important repressed material. The analyst, seeking the true dynamics, disputes the reliability of material obtained under drugs because of the influence of suggestion. When patients are amenable to suggestion, however, they can be directed towards the suppression of psychotic ideation.

The following four cases demonstrate the effectiveness of directive psychotherapy with the goal of suppression of psychotic thinking.

Case #1: M.E., a 39-year-old, single male, had been hospitalized since February 4, 1953, with a diagnosis of schizophrenic reaction, chronic, undifferentiated. Early history is non-contributory, except for malaria while in service. He completed high school, spent three years in the Army, attended business college for a few months and farmed thereafter.

Mental illness appeared in 1950 when he suddenly left his work in the field because he felt a neighbor was going to shoot him. He became withdrawn, behaved in a bizarre and silly manner and complained of loss of memory. He was hospitalized only when he became upset, belligerent, flighty, irrelevant, and had the delusion that he would be elected President since President Eisenhower was a foreigner born in Poland. He was treated with insulin, EST, and various tranquilizers. Recently he had a three-month course of chlorpromazine with up to 2000 mg. daily and subsequently a course of

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trifluoperazine up to 60 mg. daily without results. After six years of hospitalization, he was described as a severely regressed schizophrenic, completely out of contact, who rarely talked. When interviewed he would say he was never born but came out of a dirt hole. He had no name, but admitted his identity when called. He talked irrelevantly in symbolism i.e., "I am here for T-body, this is G-house on Y-land, X-letter," etc. He denied any relationship to his next of kin, particularly mother and sister with whom he had lived. He claimed his body was made of silver and his head of wood. He was hard of hearing because his head was "screwed on wrong."

During the first intravenous Ritalin treatment patient repeated these statements but when told they were delusions, he acceped the suggestion. In fact he responded well to directive psychotherapy. Because he claimed total amnesia for his past life experiences, his personal history was made known to him and he was instructed to memorize it. During the treatments which followed he became coherent and relevant, acknowledged the fact that he was human, that his body was "flesh and bone" and he repressed his symbolisms. Subsequent rehabilitation with occupational and educational therapy followed. Psychological tests verified improvement which was lasting. Patient, though still in the hospital, is scheduled to leave on trial visit.

Case #2: D.S., a 45-year-old, male patient had been hospitalized since November 30, 1951 with a diagnosis of schizophrenic reaction, paranoid type. Early history was uneventful except that at the age of 9 he lost his father. He completed the 8th grade, was married in 1938 and divorced in 1950. He has two children. Mental difficulties began during his two years of service in the Marines, 1942-44. He had difficulty adjusting to groups and felt his fellow soldiers were reluctant to expose themselves before him being aware of his homosexual guilt. He became acutely psychotic, experienced auditory hallucinations, was hospitalized, and later discharged from Service. He worked the next four years as a laborer in a packing plant where he had been employed previously. He again became acutely psychotic, heard voices, had visions of Christ, and had to be re-hospitalized. He did not respond to insulin, EST, or tranquilizers but regressed, became apathetic and totally unmotivated. He was asocial, would not participate in any activities, and refused to communicate with anyone.

Under intravenous Ritalin he became over-talkative, the psychotic process was reactivated with many bizarre delusions. He stated he was never born but was created 7 or 9 trillion years ago "as anybody else." He came from another planet in outer space, traveling by space ship. Since landing, he has been Commander in Chief of the U.S. Army and special agent and under-cover man for the FBI. He doubted he was human and denied relationship to his next of kin. A secret power controlled his mind. Ritalin treatments brought out the same content of thought. However, he slowly followed suggestions offered under directive psychotherapy and his mood and affect improved markedly. Subsequently his behavior improved, he became more active and sociable. He finally requested work assignment and most psychotic ideas were repressed. He is still in the hospital.

Case #3: B.S., a 37-year-old, white, married, male had been hospitalized since December 24, 1957, with a diagnosis of schizophrenic reaction, chronic, undifferentiated type. He is an individual with low mental endowment who had achieved an 8th grade education. A half-sister is mentally ill and has been hospitalized for many years. He lived on a farm until age 21, served in the Army three years, was in active combat 10 months. After service he worked for several years as a construction laborer and for 9 years prior to his hospitalization, as a school janitor.

Three years ago he married a woman five years his senior. He became very dependent on her mainly because he felt she was intellectually superior. His first somatic complaints started while in combat. He said he would be apt to put his hands up and start running when the fighting got too close, and he would vomit. Since 1945 he has been somewhat sickly, possessing little physical or mental energy. He was hospitalized twice for pneumonia, subsequently for pleurisy, pulmonary TB, duodenal ulcer, sinusitis, hepatitis, appendectomy, anal fissure, hemorrhoids, malnutrition, and spastic colon. Asthenia and multiple somatic complaints initiated the history of mental complaints which did not enable the treating physician to establish a diagnosis of psychotic reaction. Present hospitalization was due to acute psychotic symptoms. He had become increasingly withdrawn, blocked and catatonic. He had religious preoccupations, believed the Lord's spirit had left him. Although treated with metrazol, iproniazid, meprobamate and phenothiazines, patient was a totally withdrawn catatonic who was practically mute and did not participate in any rehabilitation program.

Intravenous Ritalin produced a dramatic abreaction which lasted several hours. He expressed guilt feelings about his mental illness which made him unable to associate with people and to do his work. He felt that the treatment was successful because Jesus saved him and he was reborn. He admitted to auditory hallucinations which he had denied before. Following the initial treatment he became approachable at all times, ,participated in ward activities, was normally talkative and improved so much in the next six weeks, during which he received several more Ritalin treatments with directive psychotherapy, that he was able to return to his previous job as a janitor. After one year patient is still reported to be doing well.

Case #4: A.M., a 34-year-old white, single male hospitalized several times between 1954 and 1957,

prior to his present admission May 1959. Diagnosis was schizophrenic reaction, paranoid type each time. Childhood and adolescence were uneventful. He went through high school but did not receive a diploma because he failed in English. He served in the Armed Forces from 1944 to 1948; work record since has been spotty and consisted of common labor and odd jobs. History of alcohol, though contributory, is not a main factor. Symptoms were vague ideas of reference, persecution, inadequacy and intense fear. Previous treatment with EST, insulin, and tranquilizers resulted only in partial recovery each time. Relapses followed due to his inability to adjust socially and economically.

Under intravenous Ritalin, psychodynamically important information was obtained which previously could not be elicited. The patient commented that he wanted to communicate the following to other physicians but was never able to do so. He expressed beliefs that certain events were responsible for his illness. At age 5 he fell out of a moving car and hurt his head. Because of this accident, his mother forbade him to participate in sports. This was partially responsible for his poor adjustment in school. At age 11 he was punished unjustly by a teacher who believed he was cheating, although he was merely asking a classmate to tell him what was written on the blackboard because he couldn't see it. He was made to kneel on coal near a hot stove for one hour. This caused him to resent the teacher, the school in general, and contributed to his poor scholastic adjustment. At 17 he committed bestiality with sheep and other animals and had incestuous relations with two younger sisters, age 9 and 14. During that year he was struck mildly by lightning and thought God was punishing him for his behavior. In 1947, after leaving the train at Hiroshima, while on furlough, he felt a heat wave invade his body and heard the voice of God admonishing him for his sin. Later he rationalized he may have been affected by A-bomb radiation. Since then he heard voices but never admitted it to his treating physician. To overcome his fears and guilt feelings, he resorted to periods of drinking and was unable to adjust and remain gainfully employed. Material elicited was used for directive psychotherapy. He was relieved of his guilt feelings and fears of punishment and a major change was seen. He was discharged from the hospital and has made a good adjustment.

Summary

In the advanced schizophrenic, non-directive psychotherapy as practised by the analyst is frequently of no avail because no rapport can be established or the patient continues to indulge in his fantasies. Directive psychotherapy as used by the organically oriented therapist is greatly facilitated by the use of cerebral stimulants which improve mood and affect and make the patient more amenable to suggestion, a factor of great importance in the directive method. Four case reports are presented which illustrate the action of intravenous Ritalin (methylphenidate), cerebral stimulant and antidepressant.

Author's Note: The drug Ritalin, used in this study, was generously supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

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Observations on Persistence of War Neurosis

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Experimental "neuroses" produced in lower animals have afforded opportunities to study the development and persistence of autonomic and behavioral changes associated with the experimentally induced illness.[1,2] The production of these neuroses is brought about by the forcing of discrimination beyond the capacity of the animal or by subjecting it to excessively strong excitation or by requiring the animal to exert intense or protracted inhibition.[1] The animals respond to such situations with neurotic signs which may appear transitorily or may persist for the life of the animal.[2] Accompanying the behavioral signs of the neurosis are autonomic changes particularly in cardiac, respiratory, sexual, and excretory functions.[2] Pavlov[1] and Gantt[2] have implied a genetic predisposition to the development and persistence of the neurotic signs when the animal is subjected to the experimental procedure.

Combat experience had all of the elements necessary for the production of conditional reflexes. In addition, the training received by the soldier was in itself a conditioning experience. The sounds and sights associated with combat served as the conditional stimulus. The unconditional responses were those associated with self preservation, either aggressive fighting back—or flight, which included taking cover, or retreat. Thus, if severe conflicts arose as a result of repeated battle experience, discrimination might have been forced beyond the capacity of the individual. Prolonged inactivity necessitated by the battle situation, such as occurred frequently in the South Pacific fighting, resulted in protracted inhibition. Excessive excitation occurred as a result of near misses from artillery fire or from repeated combat experience in which death appeared imminent. Although Pavlov[1] recognized the similarity of the neurosis experimentally produced in animals to war neurosis, to our knowledge no investigations have been carried out which attempted to correlate the findings in this illness with experimentally induced neuroses in animals. This study was undertaken to establish such correlations.

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Subjects and Method

There were 31 subjects in this study. They were all physically and electroencephalographically normal adult males were divided into three groups as follows:

Group I Controls: Ten men who had never been in combat. All were university students, ranging in age from 21 to 29.

Group II "Compensated" Combat Veterans: This group was comprised of 13 veterans who had combat experience; one was in World War I, six were in the Pacific Theater in World War II, four were in the European Theater during World War II, and two were in the Korean conflict. Their ages ranged from 29 to 61. All of this group are apparently making a satisfactory social adjustment as manifested by regular work habits and the absence of signs of psychiatric disability.

Group III "Decompensated" Combat Veterans: This group consisted of eight patients from the Psychiatric Service of the Durham Veterans Administration Hospital who had been in combat and whose psychiatric symptomatology dated from the time of the combat experience. Members of this group had unsatisfactory work adjustments and had presented themselves at the hospital with complaints of psychiatric symptomatology. Their symptoms were considered typical of combat neuroses as described by Hohman.[3] None of these patients was considered to be psychotic. Seven of these veterans were in the Pacific Theater and one in the European Theater during World War II. Their ages ranged from 32 to 52.

Electroencephalographic studies were carried out using Silver-silver chloride electrodes which were applied to standard head positions in the frontal, central, parietal, and occipital regions. Bipolar recordings were used in all cases. Both EKG and respiration were recorded on the electroencephalographic record.

The experiments were carried out in a quiet, darkened room. The ambient noise level was low. Extraneous noise from adjacent areas was barely perceptible in the laboratory. Following the application of electrodes the patient was requested to lie on the examining table in the recording room. The EKG electrodes and pneumotachygraph were applied.

The subjects were not told the nature of the experiment in advance except that recordings of brain waves, pulse, and respiration would be made. After the recording appeared satisfactory, there was a five to seven minute baseline recording period. At the end of this period the subject was told that a tape recording of combat sounds would be played and that it would be discontinued at any time that he might choose. The tape recording lasted approximately eight minutes. It consisted of sounds of an artillery barrage, small arms fire, and aerial bombardment. During the second half of the recording single light flashes fom a photic stimulator were added, most of these being synchronized with the sounds of exploding shells or aerial bombs. After the completion of the recording, the subjects were interviewed in an effort to evaluate their reactions to the experiment.

The tracings were divided into three periods: baseline, recording, and recording plus photic stimulation. Where it was technically possible, pulse and respiratory rate were counted for each 30-second interval.

Using one of the parieto-occipital regions the alpha factor, i.e., the percentage of a given length of record occupied by alpha activity,[4] was computed. Alpha rhythm was considered to be present when the frequency was between eight and 12 c.p.s. and when the amplitude of such wave forms was equal to half the maximum amplitude. Records were studied and the alpha factor computed over three two-meter intervals, one in the middle of the baseline period, one at the beginning of the recording phase, and one at the beginning of the third phase. Several records (2 controls, 6 compensated, and 1 decompensated) were eliminated because of the absence of a well regulated rhythm. These records showed a mixture of alpha and fast frequencies which made analysis difficult.

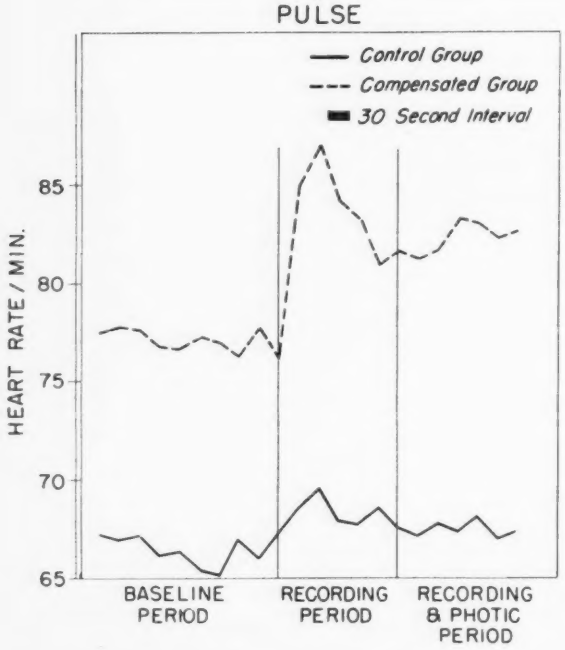
Results

Data were obtained for pulse rate, respiratory rate, and EEG changes in all three phases of the experiment for the control group and the compensated group and were subjected to statistical analysis. Because of behavioral responses occurring in the decompensated group which are described below, analysis was technically impossible.

a. Pulse. Data on pulse rate are presented in Fig. 1. During the baseline period the control group had a mean pulse rate of 66.5 as compared to that of the compensated group of 78.3 and the only slightly higher resting level of the decompensated group of 79.4. When graphs were made of individual changes it was seen that eight out of 13 members of the compensated group showed a moderate or marked increase in pulse rate during the second and/or third phases as compared to a moderate change in one out of ten controls. In terms of overall means, with the playing of the recording the control group changed from a mean of 66.5 to 69.0, a difference of 2.5 ($P=<.005$ but $>.001$). With the addition of light flashes the mean pulse rate fell slightly, i.e. 69.0 to 67.6 ($P=<.025$). The compensated group had a greater increase in pulse rate with the recording; the mean changed from 77.3 to 83.4, a difference of 6.1 ($P=<.001$). During the third period (recording plus light flashes) there was a slight decrease from 83.4 to 82.2 which was not significant ($P=>.20$ but $<.30$). A comparison of the mean increase in pulse rate in the control (2.6) and the compensated group (6.1) shows that there is a significant difference ($P=<.01$ but $>.005$). Data are limited in the symptom-

atic group; however, inspection of the individual graphs demonstrates at least a transitory increase, marked in most cases, in six out of eight subjects.

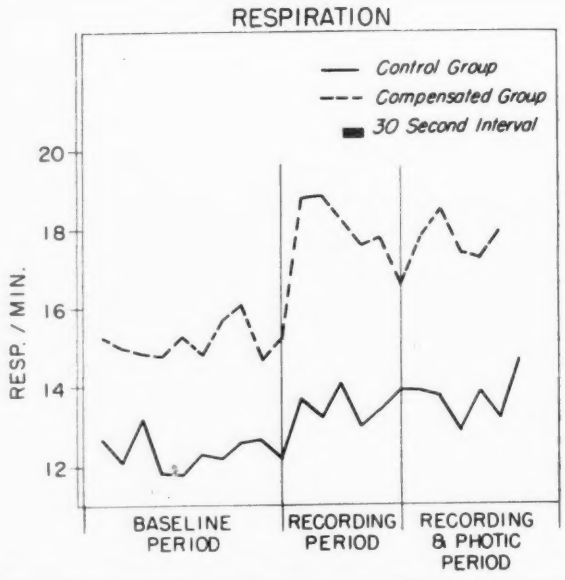
Fig. 1



b. Respiration (Fig. 2): During the baseline period the control group had a mean respiratory rate of 12.3; the mean for the compensated group was 15.3 and for the decompensated group 20.5. Individual results with the playing of the recording showed at least a slight change in six out of 10 controls, 12 out of 13 of the compensated group, and in all of the decompensated group where observation was possible. In some of the decompensated group the change was a decrease in rate. In terms of means, the control group showed an increase of only 0.8 respiration per minute whereas the compensated group had a mean increase of 2.8. The difference in the mean increase in the two groups was significant (P=<.001). The addition of photic stimulation to the recording produced no significant change in respiratory rate in either the control (P=>.20) or the compensated groups (P=<.30).

c. EEG Responses (Fig. 3): During the baseline period the alpha factor for the three groups was computed as follows: control

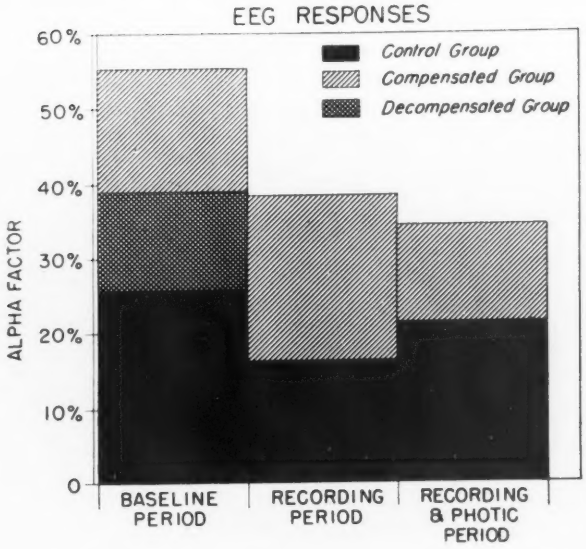
Fig. 2



group 25.8%, compensated group 55.6%, and decompensated group 38.9%. During the first part of the recording period the control group showed a significant decrease in alpha rhythm when compared to the baseline period, 25.8% down to 16.3% (P=<.025 but >.01) or a decrease of 37%. The compensated group showed less of a fall in the alpha factor than did the controls, 55.6% down to 38.4% (P=<.01 but >.005) or a decrease of 31%. During the third phase the control group had an alpha factor of 21.3% (P=<.02 but >0.1), almost a return to the baseline level. The compensated group during the third phase showed a further slight drop to 34.4% which for this group was less than either the baseline (55.6%) (P=<.001) or the recording (38.4%) (P=<.40) phases. The average number of photic stimuli presented during the sample analyzed was essentially the same (controls 13.3—compensated 12.3) (P=n.s.).

d. Behavioral Responses: None of the control group subjects appeared overly anxious. There were no motor responses except an occasional startle reaction with the first light flashes. Typical comments about subjective reactions experienced during the recording were: "I could easily have gone to sleep." "I thought of basketball games just to have something to do."

Fig. 3



Of the 13 subjects in the compensated group only one requested that the recording be turned off although six others stated that they thought of stopping the experiment. Only four members of this group did not show obvious anxiety resulting from the experimental situation. Several of the subjects with anxiety commented on various autonomic responses, e.g., sweating, dryness of the mouth, and lacrimation. One of the veterans stated: "It was hard not to lose myself back in '43 and '44." Others spoke of wanting to get "under cover" and one subject described his feelings as those of a "helpless pawn," adding: "You want to break and run and yet you can't break and run." Relatively mild motor responses were noted such as clasping of the hands and a more marked startle response to the light flashes as manifested by muscle artefact in the electroencephalographic record.

The eight patients in the decompensated group showed a still more marked generalized response to the experimental situation than did the controls. Five of these subjects were unable to tolerate the full length of the recording, permitting it for periods ranging from a few seconds to four minutes. While the recording was being played, they exhibited behavioral responses consisting of restlessness, purposeless moving of the extremities, and even thrashing around and seemingly attempting to escape from the experimental situation. Marked sweating was noted as well as dryness of the mouth. All the members of this group appeared extremely anxious at the end of the experiment. Some were tremulous, others tearful, and three men were noted to stammer severely although speech difficulty was not marked prior to the study. One of the men, previously quite talkative, became almost inarticulate.

Discussion

From the data above it is apparent that differences exist in the mean baseline pulse, respiration and alpha factor values. The difference in pulse and respiration is probably a result of age. It was not thought that familiarity with the experimental environment played any role since all subjects in the compensated and control group worked in the hospital and most were familiar with the recording procedure and the experimental environment.

In the electroencephalogram a decrease in the quantity of alpha rhythm would be expected with the heightened mental activity. However, electroencephalographic arousal occurring as a result of the presentation of repetitive auditory stimuli might also be expected to show an extinction phenomenon with time.[5] This extinction did occur in the control group where, in spite of the added influence of photic stimuli which were expected to decrease further the alpha factor, the level of alpha activity almost returned to the base line value. In contrast, the compensated group showed a slight decrease in the alpha factor with the addition of photic stimuli. These findings would indicate a heightened alertness brought about by an intensification of the feeling that the situation was one of real danger. In support of this observation one subject commented: "The light frightened me as if it were real combat. It might therefore be hypothesized that only in the presence of a heightened affective tone did the photic stimuli produce a further reduction in alpha activity.

The remaining data obtained in this investigation show that autonomic and behavioral

responses conditioned by war experiences persist in most individuals for long periods. Their presence five to 40 years after the conditioning experience lends credence to the hypothesis that human beings develop conditioned responses to combat experiences. These responses are not determined by the individual experience but by both the ability of the soldier to tolerate stress (genetic factors) and by the sum of the combat experiences (environmental factors). The persistence of these responses is determined by the compensatory mechanisms operating in the individual.

Inspection of the data in the control group demonstrates the existence of the orienting reflex. There was an initial transitory increase in attention, pulse and respiratory rate followed by inattention and in some instances by drowsiness and sleep. However, one subject with unusual visual imagery was able to "picture myself in the situation the recording presented." The experimental groups, both compensated and decompensated, demonstrated the various phenomena described by Gantt[5] in experimental neuroses, homeostasis, positive autokinesis (constructive changes) and negative autokinesis or neurotic destructive development.

Homeostasis was most dramatically illustrated in the case of one veteran of Bataan and Corregidor who showed minimal responses to the recording and photic stimulation. Although this subject stated that he felt tense, objectively he tolerated the experiment quite well and was able to talk freely about his subjective feelings. Similar responses were noted in three other members of the compensated combat group. These men demonstrated little or no objective evidence of anxiety and their subjective anxiety was minimal (e.g., "the sounds were just like street noises"). In general, they showed less marked changes in pulse and respiratory rate than other members of the same group. The remainder of this group demonstrated positive autokinesis in varying degrees. This phenomenon was particularly noticeable in three subjects. These three veterans were able, as were the remaining members of this group, to control their behavioral responses in an appropriate manner. However, they showed marked increase in pulse and respiratory rates and described their subjective reactions in a way which indicated that they had felt, to a remarkable degree, as if they were in an actual combat situation.

Negative autokinesis was observed in all except one subject of the decompensated group where the maladaptive phenomena in the experimental situation resulted in near-psychotic reactions and in behavioral responses which precluded continuation of the experiment. These responses were, to say the least, dramatic. The degree of anxiety produced in all instances was marked and on two occasions was shared by the experimenters to a degree that the experiment was terminated before the patient requested termination.

Gantt has defined the term schizokinesis as, "not only the lack of a parallel between the general, emotional, visceral acquired responses and the specific motor habits, but the sum of all those maladaptations, such as evident inefficiency of the organism in meeting stress in the daily routine of life."[6] Although it was not the purpose of this experiment to demonstrate schizokinesis, it was apparent that other non-combat stimuli would, in some of the compensated and in all of the decompensated veteran subjects, elicit subjective feelings and autonomic responses similar to those elicited by combat sounds. Many of the compensated subjects when interviewed described symptoms resulting from air hammers, approaching trains, and airplanes. The decompensated group described symptoms in response to any sudden auditory environmental stimulus with the severity of the symptoms being determined by the degree of similarity to actual combat sounds.

Further studies are being conducted to investigate the specificity of the responses reported here, i.e. that these responses occur as a result of combat-related stimuli only in those subjects who have had combat experience. From preliminary experiments it would appear that such responses are not elicited in patients with anxiety neuroses in

whom the illness is unrelated to combat experience. In addition, the phenomena of schizokinesis are to be investigated more thoroughly.

Summary

Psychophysiological responses to a recording of combat sounds were observed in ten non-veteran controls, 13 compensated, and eight decompensated veteran subjects. Observations were made on changes in pulse, respiration, and quantity of the alpha rhythm (alpha factor) in the EEG. In addition, subjective responses were determined by interview and recorded.

The non-veteran control group of subjects showed responses compatible with the so-called orienting reflex of Pavlov.

The compensated combat group showed mild to marked physiological and behavioral (motor) responses which were considered to be manifestations of conditioned responses resulting from combat experiences.

The group of combat veterans with neurotic symptoms resulting from combat experiences showed disturbed behavioral responses which prevented the observation of physiological responses. This behavior at times was near-psychotic. Neurotic symptoms were intensified for varying periods after the experiment.

These studies demonstrate a remarkable similarity of the behavioral and physiological responses of the war neuroses to those observed in experimental neuroses in animals. The natural history of the development and persistence of the responses observed in the war neurosis is, as well, quite similar to that of the experimental neurosis. The varying length of time that the symptoms persist in both the compensated and decompensated combat veterans may substantiate Pavlov and Gantt's contention that a genetic factor is present.

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Use of Librium in 100 Private Patients

HARRY F. DARLING, M.D.

Since the introduction of Librium® (chlordiazepoxide), described by its manufacturer as a "psychosedative," the chemotherapy of psychoneuroses and agitated depressions has been revolutionized. A chemical approach to treatment of the anxiety-agitation group of illnesses is now theoretically possible. Since neurotics have not progressed as far into dynamic disorganization as have psychotics, the neurotics in general should be amenable to chemotherapy provided it is more or less specific. When relieved of anxiety, it would seem that the neurotic should be open to verbal psychotherapy and this type of therapy should be effective in a shorter time. Moreover, the prognosis in the neurotic should be better than in the psychotic. Verbal psychotherapy in schizophrenia, for example, from Freud to Arieti[1] has been described as varying from useless or harmful[2] to difficult or theoretically impossible; whereas in psychoneurosis, it is described as efficacious in many cases.

The practice of routine use of the phenothiazines in cases of psychoneurosis is controversial; the percentage and degree of improvement stated by various authors is, to say the least, inconsistent. However, a higher percentage of improvement is found in ambulatory than in institutionalized pa-

Librium®, Hoffmann-La Roche Inc.

tients. It must be remembered that in many state hospitals virtually no verbal psychotherapy is given and the patient soon leaves because he feels out of place, whereas in private practice the psychoneurotic is interviewed intensively. What part of the improvement from phenothiazine therapy in the psychoneurotic is due to verbal or situational causes and what part to chemotherapy is not known because the psychoneurotic responds to verbal psychotherapy and to situational change.

Many diagnosticians reject Bleuler's interpretation[3] of the psychoses partly because of our neo-Kraepelian diagnostic standards and partly because early schizophrenia is not considered legal insanity except in a handful of states (Durham-Pike ruling and irresistible impulse as a defense) under special circumstances. By employing the concept of the schizo-affective and pseudoneurotic type of schizophrenia, and using even more flexible interpretations of this term[2] there now seem to be two ways in which diagnostic interpretation is made. One is the usual state hospital method of classifying patients as schizophrenic only if they are frankly committable; less advanced cases are considered to be within the psychoneurotic, situational or personality disorder categories. The second method is to classify early schizophrenics as such. However, it should be noted that between the intratensive neurotic and the early schizophrenic lies a group of neurotic patients with varying degrees of schizoid personalities and manifestations. In this group are those patients relatively fixed in a schizoid-neurotic pattern and those whose neuroses are in reality the prodromata of schizophrenia.

For this "twilight" group between the frank neurotic and the frank schizophrenic, the drug of first choice should be a phenothiazine. It is felt that in general these are patients who respond adequately to appropriate dosages of the phenothiazines, and that with a few exceptions they are the only neurotics (if so classified by present statistical diagnostic standards) who do respond to phenothiazines. Such cases are excluded since this is a selective study as far as neurotics are concerned, and is limited to patients inflicted with the entity in "pure culture." The study is also limited in that the milder neurotic patient who responds to milder treatment and especially verbal psychotherapy is excluded. Therefore, the neurotics tabulated are in the majority those who are moderately or severely ill.

Librium was used as a temporary, emergency measure for patients with catatonic excitement and other fugue states. In doses of 75-200 mg. the drug was markedly effective in relieving fear, anxiety and agitation to the point that oftentimes the patient was spared commitment. However, these patients are not included in the study because the eventual longer term treatment of their illnesses was accomplished with slower acting drugs after they were quieted down with Librium.

In Table I the patients are classified by age. Duration of illness is given in Table II. Table III subclassifies according to diagnosis and seems to indicate that the drug is more effective for neurotics than psychotics.

In both neurotic and endogenous reactive depressions, more especially in the latter, the drug would work for a while in some cases until a tolerance developed. Oftentimes, after the appearance of this tolerance, an increase in dosage increased side effects to the point that they were disturbing. These patients were placed on chlorprothixene and will be discussed in a subsequent paper.

Initial dosage of Librium (a fast acting drug) was calculated according to the estimated need of the patient. The greater the fear, anxiety and agitation the higher the dose—analogous to the use of opiates for varying degrees of pain. Age was also taken into consideration. The dosage was gradu-

TABLE I

Age Distribution

Years	*%*
15 - 25	10
26 - 35	25
36 - 45	36
46 - 55	18
56 - 65	15
66 or over	8

ally increased to the point of drowsiness and/or improvement. (See Table IV.) Slight drowsiness at this optimal dose is not included in the tabulations of side effects. Incidence of disturbing drowsiness or lethargy, often accompanied by ataxia and ptosis of the eyelids, is enumerated in Table V. No case of ataxia or ptosis has been found without concomitant drowsiness. The patient with tremors, which were severe and coarse, responded to Cogentin. There was concomitant ptosis but drowsiness was minimal.

TABLE II

Duration of Illness

	YEARS				
	Less than 1	1 - 2	2 - 5	5 or more	Total
Endogenous depressions	8	6	2	2	18
Neurosis	12	20	30	13	75
CBS	1	3	3	0	7
Total	21	29	35	15	100

TABLE III

Degree of Improvement

	IMPROVEMENT					
Psychoses	Marked	Moderate	Minimal	None	Worse	Total
MD - D		1				1
MD - Mixed	1	1				
End. dep.	4	6	2	1		13
Psych. dep, react.	2	2				4
Neurosis						
Anxiety	27	10	5	2	2	46
Dissociative reactions	1					1
Obsessive-comp.	2	2	1	1		6
Reactive dep.	6	10	2	1	1	20
CBS		5	2			7
Total	43	37	12	5	3	100

TABLE IV

Dosage

Mg. Daily	No. Patients
20	2
30	10
40	21
60	20
75	18
100	19
125	1
150	2
200	6
300	1
	100

TABLE V

Side Effects

	%
Drowsiness	15
Ataxia	8
Ptosis	4
Tachycardia	2
Constipation	2
Tremor	1
Indigestion	1

Discussion

It was apparent from the beginning of this study that Librium had something more than a psychosedative action. While there may be a synaptic action with Librium similar to that of meprobamate, there is also a definite selective action somewhere in the midbrain or contiguous areas. This has been made evident in many ways. Some patients tolerated extremely high doses without sedative effects. Insomnia was often relieved by daytime dosages without drowsiness or lethargy during the day, and in some cases with increased daytime alertness. The percentage of improvement over a period of several months was consistently higher than one would expect with a "minor tranquilizer." Psychotic reactions were more amenable to therapy with the drug than one would have expected with a "minor" drug.

Of striking interest was the case of a professional man who had an orthopedic impingement of his cervical cord with onset of paralysis of the legs and of atrophy, with ataxia and extreme pain. The condition had been progressive for six months and laminectomy was considered. The patient knew the full implications of what laminectomy might do. While the neurosurgeons were debating whether to operate, the patient's anxiety crescendoed and he developed agitation, depression, and he seriously contemplated suicide because he was obsessed with the idea that he might end up as a post-operative quadriplegic. He took between 100 and

200 mg. of Librium daily with neither drowsiness nor further ataxia notwithstanding the fact that he was taking other drugs for the severe pain and he already had a severe ataxia. Yet this man could not take Sparine, which had been tried on him previously, without extreme drowsiness, lethargy and increase of ataxia, nor could he take even an ounce of hard liquor without the same symptoms. The chief of neurology of the large Boston hospital where the operation was finally and successfully performed has added Librium to his pharmacopoeia and feels strongly that the patient's sanity was saved by it.

Obsessive-compulsives are exceptionally interesting. It has been pointed out that they do respond to the drug.[4-6,8] Of six obsessive-compulsives placed on the drug, two made marked improvement. One of these patients took the drug intermittently and the other took it continuously and it seemed only to hold her condition in check. Verbal psychiatry was possible with the one but the other was not amenable to anything but reassurance. In the remaining four cases, two improved moderately, one slightly and one not at all. Only one of these patients became drowsy with Librium, and then only on doses of 300 mg. daily. These results with obsessive-compulsives seem to be a convincing demonstration that the drug is more than a minor "psychosedative."

Amenability to verbal psychotherapy is markedly increased with Librium and many hours can be saved thereby. As these patients improve they often delay, postpone or cancel appointments for the reason that they are busy with their affairs and feel so well that they put off their appointments. In many patients, especially those who improved markedly, psychotherapy must of necessity be rapid and often is incomplete. Private ambulatory patients are not captive audiences. The loquacity mentioned by Bowes[4] has been found in many cases by the writer, and even in the nonlogorrheic patient there is more accessibility. It seems that repressed memories and conflicts literally run out of some patients with little prompting. There is a propensity to removing resistance and blocks which is not attained with other drugs. This is not necessarily an attribute of the drug itself but rather a confirmation of the theory that the neurotic is more amenable to psychotherapy than the psychotic. The drug alleviates the symptoms and as a result makes the patient more amenable and receptive to verbal psychotherapy if the psychiatrist can catch him.

Summary and Conclusions

Librium was administered to a group of 100 patients. Dosage was adjusted according to the necessity of the illness present. Not unexpectedly, the large doses sometimes produced drowsiness with or without concomitant ataxia.

Librium is a remarkably effective medication for controlling the symptoms of anxiety, agitation and fear. It increases amenability to verbal psychotherapy in a significantly large proportion of cases. Judging from clinical results particularly in endogenous depressions its action seems deeper than that of a simple "psychosedative."

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The Response of Locked Ward Patients to the Change of Doctors in a Residency Program

LANE AMEEN, M.D., and JULIUS LAFFAL, PH.D.

The purpose of this study is to determine if and when symptomatic and social behavioral responses of acute locked ward psychiatric patients change significantly during the period of annual change of psychiatric residents. The study took place on the psychiatric service of a general medical and surgical hospital, in an acute treatment unit for patients requiring closed ward care. The unit is divided into two physically identical wards, each with a capacity of 20 patients. Most of the treatment is done by psychiatric residents who remain at the hospital for one year. On the first of July the residents leave and new residents arrive. The ratio of patients to resident doctors is roughly seven to one, and patients are seen an average of three hours a week in individual psychotherapy.

The observation period in this study was a four week period beginning two weeks prior to July first and extending two weeks after July first. Two observers found two group therapy sessions and two periods of free ward activity on each ward during the four week study. One of the observers was the leader in group therapy, the other participated only as an observer. During the free ward activity periods the observers sat in the day room where the patients congregated, with neither observer participating except as demanded by the behavior rating technique.[1] Immediately after each observation period each patient was independently rated by the two observers using the *Individuals in Groups, Behavior Rating Technique.*[2] The study was done in each of two successive years.

Method

Our rating technique has been described in detail elsewhere.[1,2] Briefly, it consists of a set of seven scales, each divided into five scoring intervals.

Socialization is scored in terms of initiation of contact with others, response when contacted, duration of contacts, spontaneity of interaction, and number of persons contacted.

Attitude toward authority is scored in terms of the patient's manner of relating to authority figures such as doctors, nurses, therapists or aides.

Control is scored in terms of the extent to which the behavior of the individual distracts others from the goals of the activity being pursued by the group.

Aggression relates to hostile verbalizations and physical violence which may be relevant to the group activity.

Anxiety is rated in terms of intensity, duration, and number of such manifestations as restlessness, flushing, trembling, verbalizations of fears, crying, blocking, and nervous movements.

Involvement is scored in terms of the degree to which the individual strives to achieve the goals of the activity.

Role is scored in terms of extent to which an individual is able to assert his own point of view in the group.

A special scoring booklet makes it possible to score the patients on all the scales, in the activity under observation, in a matter of minutes. The manual of scoring examples facilitates the classification of dubious instances.

Results

The reliability of the scales under the rating technique is shown in Table I.

These reliabilities are Pearson product-moment correlations between scores given by each of the two raters to the patients observed in the group activities. The table shows the reliability of the scores in the 1956 and the 1957 studies separately, as well

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TABLE I

Reliabilities (Pearson r) of Scoring of Individuals in Groups Rating Technique, 1956 and 1957, Group Therapy, and Free Ward Activity.

Scale	1956		1957		Average	
	r	N	r	N	r	N
GROUP THERAPY						
Socialization	.85	143	.81	150	.83	147
Attitude	.84	106	.64	138	.73	122
Control	.71	145	.73	149	.72	147
Aggression	.80	143	.75	150	.77	147
Anxiety	.53	144	.57	149	.55	147
Involvement	.81	140	.87	149	.84	145
Role	.80	116	.72	108	.76	112
FREE WARD ACTIVITY						
Socialization	.79	195	.63	222	.70	209
Attitude	.59	59	.67	211	.65	135
Control	.39	195	.61	221	.51	208
Aggression	.67	210	.63	221	.65	216
Anxiety	.60	196	.59	221	.59	209
Involvement	.72	196	.64	220	.68	208
Role	.29	64	.37	90	.34	77

as the average reliability for each scale, obtained by weighing each correlation by its N and taking the average of the weighted sum. In general the group therapy data were more reliable than the free ward activity data.

Patients were free to come into and leave the group therapy room as well as the day room in which ward observations were made. Therefore, in only a few instances was it possible to obtain scores for a given patient in all of the weeks of the study. Thus, Patient A might have been observed for weeks 1, 2, and 4, Patient B for weeks 1, 2, and 3, and Patient C for only weeks 2 and 3. Because of this uneven distribution of observations data were analyzed by means of a *t*-test for related measures using only the scores of patients present in adjacent weeks. The comparisons made were for week 1 versus week 2, week 2 versus week 3, and week 3 versus week 4. A patient's score on any scale for a particular week was the average score either of his group therapy or his free ward activity scores for that week.

Table II shows that scoes in week 2 were lower than scores in week 3. By and large, week I scores were also elevated as compared to week 2.

TABLE II

Comparisons of Scores

	Week I vs. Week II		Week II vs. Week III		Week III vs. Week IV	
	1956	1957	1956	1957	1956	1957
GROUP THERAPY						
Socialization	1	1	3	3	4	3
Attitude	1	1	3	2	3	4
Control	2	1	3*	2	3	3
Aggression	1	1	3*	3	3	3
Anxiety	2	1*	3	2	4	3
Involvement	1	1	3	3	4	3
Role	2	1	3	3	4	3–4
FREE WARD ACTIVITY						
Socialization	1*	2	3*	3*	4	3
Attitude	–†	1–2	–	3	–	4
Control	1	1	3	2	4	3
Aggression	1	1	3	3*	4	3*
Anxiety	1	1	3*	3*	4	3
Involvement	1	1	2	3*	4	4
Role	–	1	3*	3*	–	–

*Mean significantly higher than mean of adjacent week at .05 level or better by *t*-test.

†Not enough scores obtained to be useful.

The intercorrelations of the various scales used in the study appear in Table III. These correlations are averaged over both raters and over the two years of the study. Table III shows that the scales, with the exception of Role and Socialization, were relatively independent of each other.

TABLE III

*Average Intercorrelations (Pearson r) of Scales**

	Att.	Contr.	Aggr.	Anxi.	Involv.	Role
Socialization	.34	.23	.51	—.08	.58	.71
Attitude		.26	.42	—.05	.27	.37
Control			.56	.24	.02	.28
Aggression				.19	.33	.57
Anxiety					—.08	—.08
Involvement						.63

*These averages are taken over four sets of correlations, the correlations for the two raters, in the two separate years of the study.

Discussion

Week 2 of the study, the week immediately preceding the departure of the old residents, revealed the most striking changes. It was a week of general reduction of social and symptomatic behavior on the part of the

patients both in group therapy and the free ward situation. Week 3 of the study, the week following the departure of the old residents, and the arrival of the new residents, showed a general upsurge of activity which was especially marked when the scale scores were compared to those of week 2.

A comparison of the changes which took place in group therapy with those that took place in free ward activity is of interest. In group therapy it was only in the 1956 study that week 3 was significantly greater than week 2. The differences were in the Control and Aggression scores. In the 1957 study there were no significant differences in group therapy for weeks 2 and 3. On the other hand in the free ward situation Socialization, Anxiety, and Role all showed increases for both 1956 and 1957, and in addition, in 1957, Aggression and Involvement showed increases in week 3 as compared to week 2. One possible explanation of the difference between group therapy and free ward behavior is that the group therapy in both years was led by the ward psychologist and attended by the ward chief, both of whom were well known to the patients. The opportunity to interact with permanent senior staff during the period of transition may have had the effect of damping the changes which were observed in the free ward situation where no such interactions occurred.

Some week 4 scores were significantly lower than week 3 scores, and some week 1 scores were significantly higher than week 2 scores. This would suggest that weeks 1 and 4 were weeks of relative *status quo,* and that the critical responses occurred in weeks 2 and 3, the week immediately preceding and immediately following the change of resident psychiatrists.

We speculate that the behavioral changes in week 2 were related to the imminent loss of significant figures, the therapists. The patients may have been attempting to hold on to their doctors by demonstrating "good behavior" and independence of other patients. We may also speculate that the findings of week 3 were due to the interaction of two factors: the actual departure of the familiar therapists, and the arrival of new, unfamiliar residents. The behavior which had been inhibited in the last week of the old therapist's stay was given expression since there was no longer danger of retaliation by him. In addition, the increased aggressivity, acting out, and anxiety may have served to define the limites of the new regime, while the increased socialization could well have reflected the search by patients for mutual support in a threatening situation.

Summary

The purpose of this study was to examine the symptomatic and social behavioral responses of acute locked ward psychiatric patients to the annual change of psychiatric residents. Patients were observed in group therapy and free ward groups, during the period of resident change. Ratings were made on scales of Socialization, Attitude toward Authority, Control, Aggression, Anxiety, Involvement and Role in the group.

The study was done in each of two successive years. The duration of the study in each year was four weeks, two preceding and two following, the residents' departure. Two identical closed acute psychiatric wards, each containing 20 patients, were studied simultaneously.

Patients exhibited significantly lower scores in Socialization, Aggression, Anxiety and Involvement in the week immediately preceding the departure of the residents. Conversely, there was a significant increase in such scores in the week immediately following the departure of the residents. The changes were more evident in free ward activities than in group therapy.

Authors' Note: This paper has been reviewed in the Veterans Administration and is published with the approval of the Chief Medical Director. The statements and conclusions contained in the paper are those of the authors and do not necessarily reflect the views of the Veterans Administration.

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Absence of "Trial Response" in Aged Chronic Psychotic Patients

JOHN R. WHITTIER, M.D.

In the course of clinical trial of an animal extract, a group of aged, chronic psychotic patients received capsuled material by mouth and were observed in a design providing screening observations with minimal stimuli by the medicating process, the observing process, or both (together termed "trial stimuli"). This reports the methods and results of this experiment.

Materials and Methods

Selection of Patient Population: Twenty females were selected from a population of approximately 700 patients in R building of Creedmoor State Hospital. Selection criteria were: age 60 or over, ambulatory, continuous hospitalization over one year, ability to speak in English, and mental status including defects in memory, judgment, and orientation. The clinical diagnoses for the group were as follows: dementia praecox—11, manic-depressive psychosis—3, psychosis with cerebral arteriosclerosis—1, involutional psychotic reaction—1, psychosis with senility—3, and psychosis with epilepsy—1. The group was thus composed of aged patients, with different diagnoses and a high mean duration of continuous hospitalization since admission (19 years). All patients remained on their ward in the Continued Treatment Building, without segregation.

Administration Characteristics: The capsuled material, given t.i.d. p.o., was administered by nursing discipline of the research unit. The extract and placebo fluid capsules were practically indistinguishable, and were not identified to patients or observing personnel. Medication was begun on the day after the pre-trial observation, and continued daily until termination of the project four months later. After administration, the oral cavity of each patient was checked with a tongue depressor to insure that ingestion took place. The capsules were offered simply as "your medicine"; patients accepted administration without question, and reassurance and explanation were not necessary.

Observational Characteristics: Observations were selected in a series of conferences between discipline heads in the research unit, to provide screening reports of physiological, emotional, mental, and social status with a minimum of subjective observer distortion. Although prior studies with the extract under study had suggested an increase in motor activity and initiative might be expected, and certain observations were specifically defined for relevant phenomena, the study screen was kept as broad as was feasible. The disciplinary assignments, observations, and methods were as follows:

Psychiatry—Mental status, by verbal inquiry (sound-tape recorded) to patient from 12-item mental status questionnaire (available on request), with recording of correct-incorrect responses scored as percentage of 100 correct.

Psychology—Figure drawing and Wechsler-Bellevue II, routinely scored.

Physiology—Weight (pounds); temperature (degrees F.); pulse (count per minute); blood pressure (systolic/diastolic, mm.Hg.); blood count; urinalysis.

Nursing—Ward activity and interpersonal behavior, by response of ward supervising nurse to 20-item questionnaire (Yes and No).

Neurology—Movement speed and reactivity level, by recording of situational behavior (sound motion picture) and judgment of verbal and activity characteristics (as changed or unchanged).

On observation days, which were always Thursday, ward personnel provided a series of rooms and nursing discipline passed the patients individually in sequence from one discipline to another; by this plan, 20 patients were examined by the five disciplines in two to three hours.

The first patient contact with the observing personnel (except for a casual prior inspection by project coordinator) was on the

From Creedmoor State Hospital, Queens Village, New York, H. A. LaBurt, M.D., Director.

day of pre-medication observation. The intervals between successive observations were lengthened, to permit detection of early changes, permit relatively long-term administration, and minimize the effect of experiential variable; interval durations were 4, 14, 21 and 77 days during the four month period of the study. The only contact by patients with project personnel other than nursing was during the observations.

There was no communication between observing personnel concerning observations until a conference was held following the fourth observation period, in which all reports were reviewed. Although it was apparent that no changes had taken place, administration was continued for an additional period of months to insure no later changes would be missed.

Results

Five patients refused to accept administration during the study, so that there was a total of 15 patients in the treated group (7 receiving extract and 8 placebo fluid) and five patients in the untreated group.

No changes indicating an effect caused by the act of administration of the capsules were observed in the 15 treated patients.

Discussion

A recent review of placebo literature indicated no published reports had appeared in which absence of placebo reactivity was shown.[1] It is apparent from this study that the design reported either minimized medicating process stimuli (including the placebo stimulus) by suggestion and the complex observing process stimuli,[3] or that response to these stimuli (termed "trial response") is minimal or absent in the chronic psychotic elderly.

That older neurotic patients are less responsive to placebo stimuli was suggested in another report[5] which showed an average age of 42 for patients without response, and 32 for patients with complete recovery during placebo administration.

The considerable recent psychiatric and psychological literature on the placebo process[1] could be fruitfully supplemented by study of the observational process. An early example of a study in industrial psychology relevant to clinical trial phenomena was that reported from the Hawthorne plant of the Western Electric Company in 1939,[4] where worker behavior was found to be more dependent upon individual response to the stimuli of observation than to the stimuli of the experiment per se. Lasagna has recently drawn attention to the importance of the operational characteristics of clinical trial.[2]

The simultaneous multidisciplinary screening methodology, as described, proved satisfactory, efficient, and quasi-quantitative in evaluating characteristics of the individuals in the group. The value of standardized observational techniques was reaffirmed.

Summary

Administration of capsuled material orally, with limited "trial stimuli" (Minimal suggestion, and observation characterized by standardization, relative infrequency and brevity) effected no change in 15 aged chronic female psychotic patients over a period of four months. Either trial stimuli were inadequate to effect change, or trial response was absent in patients having these characteristics. The advantages of simultaneous multidisciplinary observations, including sound tape and sound motion picture recordings, were cited.

Acknowledgments: Collaborators included L. W. Shankel, M.D. (Psychiatry), S. R. Graham, Ph.D. (Psychology), CoTui, M.D. (Physiology), and E. Jacobi, R.N. (Nursing). The assistance of R. Herland, M.D., Supervising Psychiatrist, and of the staff of "R" Building, Creedmoor State Hospital, is acknowledged.

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A Joint Meeting Held in Tokyo Japan

(Eastern Psychiatric Research, the Kanto Neuropsychiatric, and the Japan Mental Hospital Associations)

Experiences in Drug Therapy with Trifluprомazine (Vesprin)

TAIEI MIURA, M.D., KCHEI SATO, M.D., JUN TOMINAGA, M.D., and HIROSHI SATOWA, M.D.

Trifluprомazine has been widely employed in the treatment of various psychoses, often with results superior to those obtained with chlorpromazine. The drug was administered in a small series of cases after electroshock and other pharmacological products had proved ineffective. It is not our intention to present a statistical report since this series is small. It is, however, of interest to report the results obtained with this neuroplegic because the effect was so dramatic.

Representative Cases

Case 1: A 12-year-old girl had been bradyphrenic, autistic and relatively mute for over two years. In the previous year she had been diagnosed as having childhood schizophrenia. Electrostimulative treatments were given without effect. She was thereupon hospitalized. At this time she appeared completely mute and negativistic. It was not possible to make contact with her by any means.

Initially chlorpromazine was given with no change except increased drowsiness. Trifluprомazine was then employed in initial doses of 25 mg. per day gradually increased to 50 mg. per day. After four days she began to smile. Eight days after the start of this therapy she spoke spontaneously and participated in play with nurses and other patients. She was no longer autistic and appeared almost hypomanic. On closer observation, however, her fundamental schizophrenic pattern seemed unaltered as she did not speak about her own feelings nor show any insight into her illness. The amelioration of her autistic attitude was therefore only superficial.

While it cannot be said that trifluprомazine cured the childhood schizophrenia it certainly appears that it had a remarkable effect upon symptoms which hitherto had not responded to any other means of treatment.

Case 2: A 20-year-old male patient was hospitalized in April 1959 with symptoms of schizophrenia. Electro-stimulative therapy had no effect upon the syndrome. Intensive insulin shock therapy induced remission. After a short period of convalescence he returned to his home and within four months he engaged in his former activities. The remission, however, did not endure so that in February 1960, the symptoms reappeared with an additional element of stupor. Ten ECT's were ineffective.

The patient was transferred to our clinic. Vesprin was administered, initially at 25 mg. per day and then progressively increased to doses of 125 mg. After five days of drug therapy the patient showed change in his psychomotor attitude. He became more active and after two weeks of treatment he began to answer questions though he still presented a flattened affect. After one month he spoke voluntarily to other patients and even became facetious in his relationships with the nursing staff. His remission was so dramatic that it was thought possible to reduce dosage.

The amount of trifluprомazine was progressively reduced over a period of ten days until he was entirely without the drug. Symptoms abated for about one week but then recurred. He was thereupon given the drug again and his behavior again changed suffifficiently so that he was able to return to his home. Since then he has been kept on maintenance therapy and has been functioning effectively.

Case 3: A 29-year-old Roman Catholic seminary student had developed delusions of reference in April 1959. He felt that he was being spied upon by his superior and that he was being exposed to temptation. He was hospitalized toward the end of 1959 and was treated over a period of three months with electro-stimulative therapy, drug therapy, including chlorpromazine and then insulin shock therapy. His paranoid symptomatology did not subside. A grave prognosis was given.

Encouraged by previous dramatic effects with the administration of Vesprin, it was decided to give him the drug. Within three weeks he underwent considerable change. Not only did his paranoid symptomatology disappear but he began to develop insight into the nature of his delusions. Vesprin therapy was continued for four more weeks. Finally he was discharged and returned to the seminary. Three months after the discontinuation of the drug he continued to be in good condition.

Case 4: A 34-year-old nun was admitted with a diagnosis of schizophrenia, paranoid type. The onset of her disorder began in April of 1959. She complained that she was being persecuted by other nuns. Life among the group had become progressively more difficult for her and her relationships had deteriorated progressively. She was hospitalized in May and was immediately given Vesprin, in initial doses of 25 mg. per day, progressively increased to 125 mg. per day. Since she was somewhat drowsy on this dosage, it was reduced to 100 mg. daily. Within three weeks hallucinations and delusions disappeared and her attitude toward her

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The drug trifluprомazine used in this series is manufactured by E. R. Squibb and Sons under the tradename Vesprin.

Papers presented at the Japanese meeting of the world tour of the Eastern Psychiatric Research Association have been published in the November and December issues of *Diseases of the Nervous System.*

fellows became more normal. After one month on this therapy, the dose was reduced one half without any recurrence of symptoms. Other than three electroshock treatments at the time of admission, no other treatment was given.

At the outset prognosis appeared extremely grave and one would have turned toward insulin shock to produce amelioration of her symptoms. It was, however, noteworthy that the grave prognosis was altered by the drug therapy.

Case 5: A 30-year-old schizophrenic individual suffered from delusions of persecution for six years. All forms of therapy including electro-stimulation, insulin shock and drug treatment with chlorpromazine and reserpin were ineffectual. There was no evidence of intellectual deterioration. The diagnosis of paranoid schizophrenia was confirmed after a prolonged period of observation. He was then given vesprin.

Within two weeks he developed side effects of a parkinsonian nature consisting of some difficulty in swallowing. Treatment, however, was continued. Within one month he became indifferent to his delusions. He said, "Now I am not preoccupied." Interruption of drug therapy after 45 days did not cause a recurrence of symptoms. The side effects of therapy disappeared and his improvements persisted.

In this instance,, it cannot be said that the patient developed true insight into his mental disorder. However, through six years of observation and treatment, no remission had occurred until the patient was put on Vesprin therapy.

Although our experiences with Vesprin are somewhat limited it seems that the drug is a valuable adjunct in the treatment of resistant schizophrenia provided the patient is not deteriorated and does not show deterioration in his intellectual capacity.

Treatment of Depression in Relation to Suicidal Attempts

AKICHIKA NOMURA, M.D.

Mental depression is a constant problem in daily treatment in a psychiatric practice. Much research on this subject has been done from the biological, pharmacological and psychopathological points of view. Our medical school has been active and is well recognized for its accomplishments in the fields of psychotherapy with neurotic patients. Many of these cases, however, do not respond adequately to present forms of therapy. It has been found that in these instances they present a larval type of depression.

While a typical depression presents no problems in correct diagnosis, the larval type may be masked by neurotic symptoms so that it may escape notice. Such a patient may visit the general practitioner and the specialist for a long time without change. The patient travels from one clinic or physician to another developing a sense of hopelessness and helplessness. Having encountered many individuals of this type, it was thought worthwhile to do a statistical study of this entity.

From 1948 to 1958, 1,264 cases (9.4%) were diagnosed as manic-depressive psychosis out of a total of 13,442 patients seen in our out-patient department (Table I). Many authorities believe that a reliable statistical study can be carried on only on the population in mental institutions. Therefore, we proceeded to investigate our admissions to the Negishi-Kunitachi Hospital and the psychiatric division of the Jikei-School of Medicine.

Endogenous depression constitutes 45.9% of depressed cases at our clinic and 30.3% of those at the Negishi-Kunitachi Hospital. The total rate of reactive depression is 11.1% and 18%. The involutional type of depression was 11.8% at the Jikei clinic which is rather low as compared to the other types of depression.

The sex distribution of depressive patients was analyzed. According to statistics in the U.S.A., female patients would be admitted in greater frequency than males, that is, in a proportion of 61.7% to 38.3%. Our statistics, on the contrary, show that male admissions are 53.7% as compared to female admissions of 46.1%.

According to Kraines in the United States, the age of onset of manic depressive psychosis was most frequent between 25 to 29 years in females and between 45 to 49 years in males. Our analysis would indicate that the age of onset is be-

TABLE I

Number of Manic-Depressive Outpatients from 1948 to 1958 in Jikei Psychiatric Clinic

	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957	1558	Total
Total Number of Patients	519	556	708	951	1428	1264	1498	1570	1596	1701	1651	13442
Male	32	34	43	64	73	65	88	100	81	76	80	736
Female	13	34	27	47	65	59	55	74	52	45	57	528
Total	45	68	70	111	138	124	143	174	133	121	137	1264
Rate of M.D.P. (%)	8.7	12.2	9.9	11.7	9.7	9.8	9.6	11.1	8.3	7.1	8.3	9.4

TABLE II

In-patients with Varied Types of Depression

Types	Male	Female	Total
Endogenous manic-depressive psychosis	31	15	46
Endogenous depression	37	30	67
Reactive depression	15	16	31
Involutional depression	4	8	12
Total	87	69	156

TABLE III

The Frequency of Attempted Suicide in Mental Hospitals

Disease	Attempted	Not Attempted	Suicide % Rate
Endogenous Depression	22	52	29.7
Psychopathia	6	26	18.8
Psychogenic Reaction	21	109	16.8
Presenile and Senile Psychosis	8	75	9.6
Manic-Depressive Psychosis	3	39	7.1
Schizophrenia	43	592	6.8
Epilepsy	3	42	6.3
General Paresis	4	71	5.3
Chronic Alcoholism	5	92	5.2
Drug Addiction	3	60	4.8
Oligophrenia	0	22	0
Neurosis	0	86	0
Encephalitis, Posttraumatic Psychosis, Cerebral Hemorrhage	0	53	0
Others	0	20	0

TABLE IV

Frequency of Attempted Suicides

	Total	Attempted	Rate(%)
Students	416	12	2.88
High School, Boys & Girls	258	9	3.49
Middle School, Boys & Girls	249	4	1.61
Young Wage-Earners	367	13	3.54

TABLE V

Effects of Tofranil in the Depressive State

Type	Remarkably improved	Improved	Slightly improved	Unimproved	Total
Endogenous	12	27	8	9	56
Reactive	2	4	3	4	13
Neurotic	0	1	1	2	4
Total	14	32	12	15	73

Rate of clinical amelioration (%).
Endogenous = 83%.
Reactive = 69%.

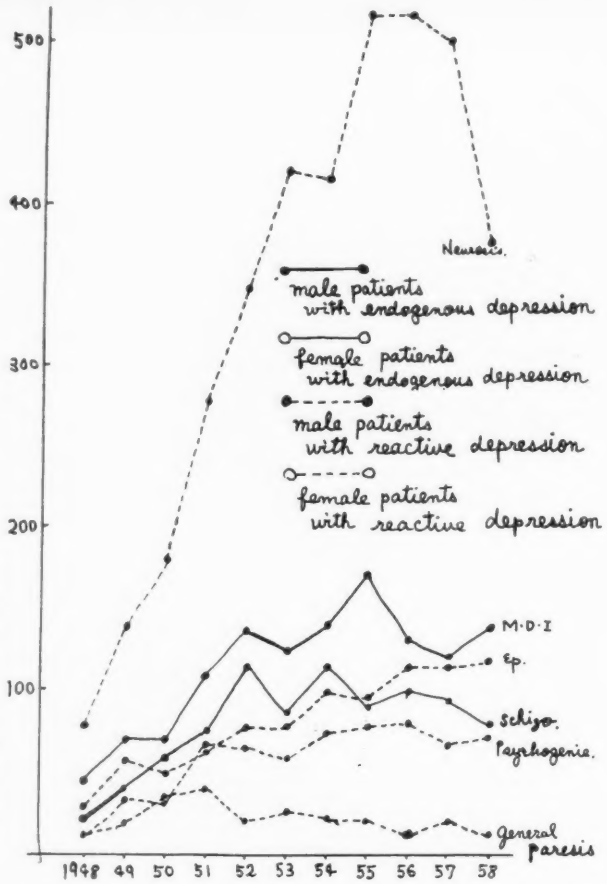

Fig. 1. Number of out-patients seen from 1948 to 1958 in Jikei Psychiatric Clinic.

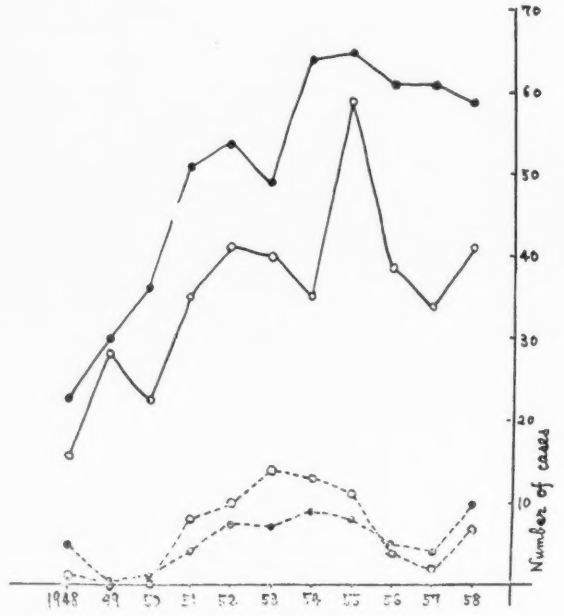

Fig. 2. Number of M.D.I. patients that were treated in Psychiatric Clinic, Jikei School of Medicine, from 1948 to 1958.

tween 26 to 30 years in both male and female individuals.

The statistical survey relative to the marital status, the order of siblings, educational history, economical status and alcohol factor is omitted.

Incidence of suicide is worthy of consideration. In our experience it has been encountered quite frequently, particularly at the early onset of the disease and during the period of convalescence. Our suicidal attempt rate was found to be 10.9%. Dr. Ohara investigated the suicidal incidence of 1457 case at two other mental institutions and observed that the incidence of suicide is most frequent in endogenous depressions and occurs in 29.7% of patients (Table III). This is a significant value when compared with the rate of other mental disorders excluding psychopaths. It may be added here that attempted suicide rate among normal individuals in contrast is below 3.5%.

The treatment of depression is worthy of brief discussion. The effectiveness of electroconvulsive treatment has been shown to be 93.8% at the Jiksei-clinic and 80.7% at the Negishi-Kunitachi Hospital. Under drug therapy with chlorpromazine, the remission rate was 33.4% but with combined drug and convulsive therapy the rate could be increased to 82.3%. Reserpine and isomytal was found to be effective in mild cases of melancholia. Imipramine brought about amelioration of symptoms in this type of patients in 83% of cases and in endogenous depression in 69%.

Recent clinical experience with Catron, a monoamine oxidase inhibitor, has been satisfactory. It has been found effective in mild cases of melancholia and in bringing about remission of symptomatology in reactive depressions.

At present a study is being made with the use of fluphenazine which is also reported to be effective in the treatment of patients suffering anxiety in connection with depression.

Depressed patients occasionally retained residual neurotic symptoms such as insomnia, agitation, unstable moods and various hypochondriacal complaints at the time of discharge after receiving pharmacological and biological treatment. In such instances adequate psychotherapy would seem to be indicated. At this point it seems desirable to emphasize the need for psychosomatic approach in order to strengthen the ego structure of such patients by means of individual psychotherapy, group psychotherapy and various rehabilitative programs.

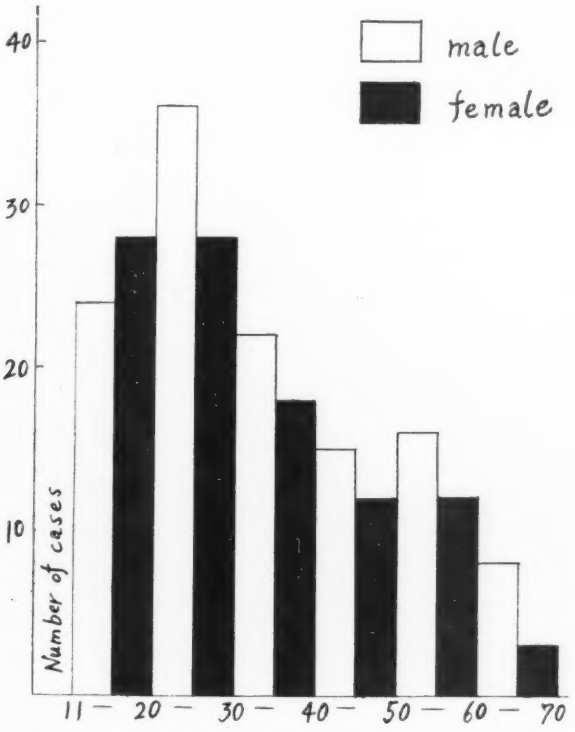

Fig. 3. Age of patient when first seen in the Jikei Psychiatric Clinic.

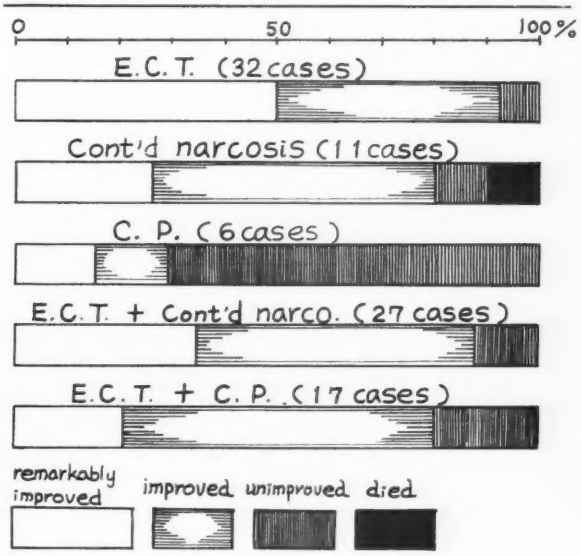

Fig. 4. Clinical effects in the treatment of depression.

Pharmacotherapy in Narcolepsy

HARUO AKIMOTO, M.D., YUTAKA HONDA, M.D., YASURO TAKAHASHI, M.D.

Narcolepsy is a unique pathological condition characterized by attacks of sleep in the daytime and of sudden loss of muscle tone following emotional excitement. Although the true pathogenesis of the disease is not clear, it is generally assumed to be due to the dysfunction of the reticular activating system.

We have been studying narcolepsy from various points of view during the past five years in the neuropsychiatric clinic of Tokyo University Hospital. We wish to report the results of our research on the pharmacotherapeutic aspect of the disease based on 80 cases that we treated. At the present time the fundamental principle in the treatment of narcolepsy is long-term symptomatic therapy. Improvement of sleep dysrhythmia accomplished by maintenance of wakefulness in the daytime, sound sleep at night, and relief from the cataplectic attacks are the main goals of the therapy.

Medicinal agents which are effective in amelioration of the sleep attacks are: caffein, amphetamine, methamphetamine, Meratran, Ritalin, Tradon and Cafilon. These drugs were effective on all narcoleptic patients to whom they were administered. Disappearance of sleep attacks could always be achieved if need be by increasing the dose except when the patient was disturbed by serious side effects, i.e. loss of appetite, loss of body weight, decrease in blood cholesterol (with Ritalin), irritation, anxiety and sleeplessness. These side effects were common to all of the drugs except Tradon which showed very few side effects, but Tradon failed to prevent the sleep attacks. It may be that the dosage of 50-120 mg. a day was insufficient. A standard method of administration was used for all the drugs: The daily dosage was divided into two parts and was given orally at 8 A.M. and 1 P.M. after meals. The dose was adjusted so as to maintain relief from sleep attacks. The drugs were all short-acting—the awakening effect did not persist to the next day. Although we found no case of addiction or chronic intoxication as the result of long-term administration, we changed the drugs every three or four months in order to avoid a possible accumulation of side effects.

Soporific drugs were given before retiring to avoid nocturnal insomnia. Addiction to these drugs was prevented by changing the drug and dosage.

While treating the narcoleptic patients for the sleep attacks, we discovered that some of these drugs were also helpful for the cataplectic attacks, and that the anticataplectic effect was different with each drug. We investigated further the anticataplectic effect of each drug (Table I). We determined the maintenance dose of a drug for each patient either by the complete disappearance of sleep attacks (marked by $+++$), or by amelioration of the sleep attacks to such an extent that the daily activities of the patient were not disturbed (marked by $++$). We determined the range of the maintenance dose and their mean values and compared the effect of the drugs on cataplexy during administration of the maintenance dose (Table II).

We used only those patients who had frequent attacks of cataplexy, usually more than one per day, in order to secure evidence of anticataplectic effect. In addition, we had the patients make daily records of their sleep, cataplectic attacks and the dosage of drugs used (Figure 1). Cafilon showed the greatest anticataplectic effect by improving 89% of patients at the maintenance dose (Table I). The mark $++$ signifies complete disappearance of the cataplectic attacks. Ritalin effected 85% improvement, Meratran 67% and Methamphetamine 33%. Although we discovered no case in which Tradon was effective against cataplectic attacks, it is possible that if we had given a higher dose, it might have proved to be effective.

Recently we investigated the effects of Tofranil (imipramine) and Catron (an MAO inhibitor), on narcolepsy (Table III). We found that

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TABLE I

Comparison of Anticataplectic Effect

Drug	Total No. of cases treated	No. cases with frequent cataplectic attacks	Effect of maintenance dose			% of effective cases
Cafilon	29	19	++	7	>	89%
			+	10		
			—	2		
Ritalin	40	26	++	4	>	85%
			+	18		
			—	4		
Meratran	28	15	++	1	>	67%
			+	9		
			—	5		
Methamphetamine	13	6	++	0	>	33%
			+	2		
			—	4		
Tradon	18	8	++	0	>	0%
			+	0		
			—	8		

TABLE II

Comparison of Maintenance-Dose in the Treatment of Sleep Attacks

Drug	Total No. of cases treated	No. of cases given effective dose	Range of maintenance dose	Average of maintenance dose
Cafilon	29	28 < 7 +++ / 21 ++	2-8 tab./day	4.5 tab./day
Ritalin	40	39 < 11 +++ / 28 ++	20-80 mg./day	54 mg./day
Meratran	28	25 < 2 +++ / 23 ++	3-8 mg./day	5.2 mg./day
Methamphetamine	13	10 < 1 +++ / 9 ++	5-15 mg./day	14 mg./day
Tradon	18	10 < 1 +++ / 9 ++	50-120 mg./day	61 mg./day

Tofranil has a very remarkable effect on cataplectic attacks. Complete disappearance of the attacks was observed in 9 out of 10 cases. To give an example, a 45-year-old woman had been suffering from severe attacks of cataplexy, more than 10 per day. She could not go shopping alone nor could she talk about anything humorous. She was easily stimulated and when stimulated became prostrated and at times would fall and suffer from dyspnea. She was completely cured with administration of 50 mg. of Tofranil, and could go to the movies by herself. This very remarkable anticataplectic effect of Tofranil takes place within one hour after initial oral ingestion and lasts a few days after discontinuance. However, Tofranil is not helpful in sleep attacks. Catron was completely ineffective in both sleep and cataplectic attacks. It is very interesting that these two antidepressants showed such an outstanding difference in their effect on cataplexy.

In a broader study we compared various drugs which are generally classified as psychoanaleptic drugs for their effects on narcolepsy (Table IV). Not all of the psychoanaleptic drugs relieve narcolepsy, and those that do, vary in their mode of action. It is observed that drugs which are effective on sleep attacks are all included in the classification of central nervous system stimulants. It seems that if a drug is effective in one case of narcoleptic sleep attacks it is effective for all these patients. This suggests the presence of an underlying pathophysiologically simple mechanism as the cause of the sleep attacks in narcolepsy. However, such a tendency is not evident in cataplexy. Besides there is no parallel between the effect on sleep attacks and on cataplexy. When we consider these facts, together with the specific effect of Tofranil on cataplexy, we are led to the conclusion that sleep attacks and cataplectic attacks are different in mechanism. Further study is necessary to clarify the specific anticataplectic effect of Tofranil. We consider that this effect is due either to the action of Tofranil as a thymolepticum in stabilizing emotional lability or to the direct action on cataplexy itself.

TABLE III

Effect of Tofranil and Catron on Narcolepsy

No. of Cases	Daily dosage	Sleep attack		Cataplectic attack	
TOFRANIL					
10	50-75 mg.	++ 0 + 0 — 10	0%	++ 9 + 1 — 0	100%
CATRON					
8	9-12 mg.	++ 0 + 0 — 8	0%	++ 0 + 0 — 8	0%

TABLE IV

Effect of Psychoanaleptic Drugs on Narcolepsy

	Sleep attack	Cataplectic attack
A. *Central Nervous System Stimulants*		
1. Caffeine; Caffeine sodiobenzoate	+	
2. Effedrine derivatives:		
Effedrine hydrochloride	+	
Amphetamine (Zedrin)	+++	+
Methamphetamine (Philopon)	+++	+
Cafilon (R381+R382)	+++	++
3. Benzhydrol derivatives:		
Meratran	+++	+
Methylphenidate (Ritalin)	+++	++
4. Oxazolidine derivative:		
5 - phenyl - 2-imino-4-oxo-oxazolidin (Tradon)	++	—
B. *Antidepressants*		
5. MAO inhibitors:		
β - phenyl-isopropyl-hydrazine hydrochloride (Catron)	—	—
Niamid	—	—
6. Thymolepticum:		
Imipramine (Tofranil)	—	+++
7. Parasympathomimetic agent:		
2-dimethylaminoethanol (Recrein)	—	—

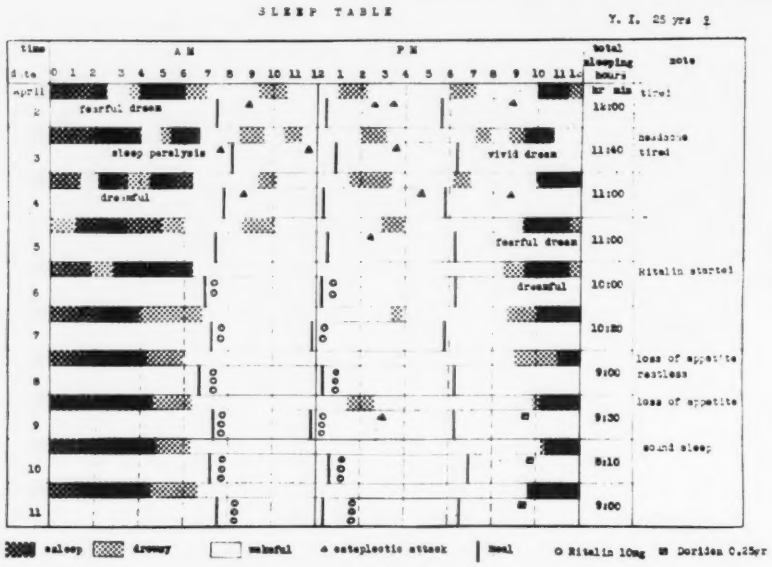

Figure 1.

For further study, we are planning to examine the anticataplectic effect of other psychotropic drugs, which have not been thoroughly tested on account of their ineffectiveness against sleep attacks.

Summary

We compared the effects of various drugs in 80 cases of narcolepsy. Drugs effective in sleep attacks are: caffeine, methamphetamine, amphetamine, Cafilon, Meratran, Ritalin and Tradon. These are generally classified as central nervous system stimulants. As far as the sleep attacks are concerned, a tendency was observed that if a drug is effective in one case, then the drug is also effective in all other narcoleptic patients, suggesting a pathophysiologically simple mechanism underlying the sleep attack.

These drugs were also effective in cataplectic attacks in varying degrees, and their anticataplectic effects were compared. Among them Cafilon and Ritalin showed marked anticataplectic effect.

Tofranil showed dramatic effect on cataplexy although ineffective in sleep attacks.

Various psychoanaleptic drugs were reviewed from the standpoint of their effect on narcolepsy.

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Speakers will be:

Anthony Sainz, M.D., Marcy, New York
Theodore R. Robie, M.D., East Orange, New Jersey
William L. Holt, Jr., M.D., Albany, New York

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